

**The Management and Outcomes of *Staphylococcus aureus*
Bacteraemia at a South African Referral Hospital: A Prospective
Observational Study**



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Preamble

Declaration

I, Nicola Steinhaus, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Staphylococcus aureus is a major human pathogen found worldwide, causing a wide variety of clinical infections. This ranges from skin and soft tissue infections to life-threatening invasive disease, such as *S. aureus* bacteraemia (SAB). Despite being a common cause of both community-acquired and hospital-acquired infections, limited evidence exists on the management and outcomes of *Staphylococcus aureus* bacteraemia (SAB) in resource-limited settings. The aim of this study was to describe a cohort of South African patients with SAB, and explore the factors associated with complicated infection and death. A prospective observational study was performed of patients over the age of 13 years admitted to a South African referral hospital with SAB. Data were analysed using Kaplan Meier survival models and linear regression models.

One hundred consecutive SAB infection episodes in 98 patients were included. SAB was healthcare-associated in 68.4%, with 57.6% of these linked to drip site infection; 24.0% of all cases were caused by methicillin-resistant *S. aureus* (MRSA). Ninety-day mortality was 47.0%, with 83.3% of deaths attributable to SAB. Predictors of 90-day mortality were MRSA (odds ratio (OR) 1.28; 95% confidence interval (CI) 1.0 to 15.1) and the presence of co-morbidities (OR 4.1; 95% CI 1.0 to 21.6). The risk of complicated infection was higher with suboptimal antibiotic therapy (OR 8.5; 95% CI 1.8 to 52.4), female sex (OR 3.8; 95% CI 1.1 to 16.3) and community-acquired infection (OR 7.4; 95% CI 2.0 to 33.1). Definitive antibiotic therapy was suboptimal in 22.6% of all cases. Overall, SAB-related mortality was high. A large proportion of SAB episodes may be preventable, and there is a need for improved antibiotic management in this setting.

Part A. The study protocol, as submitted for departmental and ethical approval, is presented here. It includes the background, rationale and methodology of the research done for this mini-dissertation.

Part B. A structured literature review is presented of articles pertaining to SAB epidemiology and treatment, with the aim to place this research study in context and identify gaps in research.

Part C. A journal-ready manuscript according to the requirements of the International Journal of Infectious Diseases.

Appendix. All additional documentation necessary as addendums in the presentation of this mini-dissertation.

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List of abbreviations

AIDS	Acquired Immune Deficiency Syndrome
BSI	Bloodstream infection
CA	Community-acquired
CI	Confidence interval
CO	Community onset
GSH	Groote Schuur Hospital
HCA	Healthcare-acquired
HIV	Human Immunodeficiency Virus
HO	Hospital onset
ID	Infectious diseases
IE	Infective endocarditis
LMIC	Low and middle income countries
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MRSA-B	Methicillin-resistant <i>Staphylococcus aureus</i> bacteraemia
MSM	Men who have sex with men
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
OR	Odds ratio
PLWH	People living with HIV
RCT	Randomised control trial
SAASP	South African Antibiotic Stewardship Programme
SAB	<i>Staphylococcus aureus</i> bacteraemia
SD	Standard deviation
SSTI	Skin and soft tissue infection
TOE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
UCT	University of Cape Town
UTI	Urinary tract infection
UK	United Kingdom
US	United States

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Part A. Research Protocol

1. Introduction and statement of purpose

Staphylococcus aureus bacteraemia (SAB) is an important cause of mortality and morbidity globally; outcomes are even worse with methicillin-resistant *Staphylococcus aureus* (MRSA), which is becoming a more frequent cause of SAB. While recommendations for the management of *Staphylococcus aureus* bacteraemia exist and are widely distributed, this disease is notoriously poorly managed. Much research has been done into the risk factors and outcomes of SAB, however very little quality evidence has been generated in a South African setting, which may have different outcomes compared with high income countries because of high rates of HIV and other infectious comorbidities.

The purpose of this observational study is to describe the clinical characteristics, management, and outcomes of patients presenting with *Staphylococcus aureus* bacteraemia in a referral hospital in Cape Town, South Africa, over the period of November 2013 to January 2015.

2. Background to the study

2.1 Introduction

Staphylococcus aureus is a major human pathogen found worldwide, causing a wide range of clinical infections from skin and soft tissue infections to life-threatening invasive disease. *S. aureus* bacteraemia (SAB) is associated with a high mortality and is a common infection in both community and health care settings. Multiple studies have documented the prevalence and outcome of SAB in high income countries, however there remains a paucity of knowledge regarding SAB in low and middle-income countries (LMIC). A global concern is also the lack of high-quality evidence to guide the management of SAB.

2.2 Clinical Burden

In higher income regions, the population incidence of SAB ranges from 10 to 30 per 100 000 person-years, with *S. aureus* being the second most common cause of nosocomial bloodstream infections in the United States (US) (Laupland et al. 2013). Large geographical discrepancies in SAB incidence likely reflect differences in health care systems, infection control practices, and the completeness of surveillance data (Van Hal et al. 2012). Healthcare-associated SAB (HCA-SAB) is associated with higher mortality, longer length of stay, and greater total hospital costs compared to bacteraemia of any other cause in the US (Shorr et al. 2006).

Less is known about the incidence and impact of SAB in relatively lower income regions such as Sub-Saharan African. It is likely comparable to high income nations, and may be higher due to the influence of HIV (Larsen et al. 2012). A systematic review of 22 studies reporting causes of bloodstream infections on the continent found the overall prevalence of SAB amongst adult patients admitted with bloodstream infections to be 5.4% (111 of 2078 isolates) (Reddy et al. 2010). At Groote Schuur Hospital (GSH), an informal review of blood cultures performed in 2012 showed that *S. aureus* was the second most common pathogen recovered after coagulase-negative staphylococci (Tina Wojno, personal communication).

2.3 Risk factors

Various patient factors affect the risk of developing SAB, with the most important of these being the presence of intravascular foreign material, such as peripheral or central intravenous catheters (Jensen et al. 1999), as well as the presence of other prosthetic material, such as joints or heart valves. Patients receiving haemodialysis are thus at a greatly increased risk of SAB (Kallen et al. 2010; Fitzgerald et al. 2017).

Extremes in age have been shown to be associated with increased SAB incidence (Laupland & Church 2014; Allard et al. 2008; Asgeirsson et al. 2011; Huggan et al. 2010). SAB is also more commonly found amongst males, with a male to female ratio of 3:2 (Allard et al. 2008; Klevens et al. 2007; Asgeirsson et al. 2011; Huggan et al. 2010), however a cohort study in Denmark showed that female patients with community-acquired SAB (CA-SAB) experienced increased 30-day mortality compared with male patients (Smit et al. 2017), suggesting gender should be considered in the triage and risk stratification of community-acquired (CA)-SAB patients.

Ethnicity is also associated with different incidences of SAB, with higher incidences on non-white populations (Klevens et al. 2007; Johnson et al. 2005; Cookson et al. 2012). Analysis of socioeconomic disparities between ethnic groups has not been shown fully to account for these differences in incidences (Tong SY, van Hal SJ, Einsiedel L, Currie BJ 2012). The contribution of host genetic susceptibility to these ethnic differences has not yet been investigated.

The HIV-infected population has a significantly increased incidence of SAB (Larsen et al. 2012; Wilson et al. 2008), irrespective of the use of intravenous drugs (Wilson et al. 2008). A lower CD4 count has been independently associated with SAB. Intravenous drug use is a risk factor for higher rates of SAB incidence in all groups, independent of HIV status (Spijkerman et al. 1996; Palepu et al. 2001; Tuazon & Sheagren 1974).

2.4 Methicillin-resistant *S. aureus* (MRSA)

The development of methicillin resistance in *S. aureus* is associated with increases in mortality, morbidity, length of hospitalisation and cost of health care (Cosgrove 2006). The contribution of MRSA to SAB has varied globally, with recent reductions shown in some industrialised nations

(Johnson et al. 2012; Cookson et al. 2012; Kallen et al. 2010; Jarvie et al. 2008; Jarlier et al. 2010), likely linked to improvements in infection control procedures. In South Africa, the prevalence of *S. aureus* infections that showed MRSA was 24% between 2007 and 2011 in state sector hospitals (Naidoo et al. 2013), and over 30% in private institutions (Brink et al. 2007).

2.5 Clinical manifestations

The presence of various primary clinical foci for SAB may be identified, with common sources being peripheral vascular catheter-related infections, skin and soft tissue infections, pleuropulmonary infections, osteoarticular infections and infective endocarditis (IE) (Tong SY, van Hal SJ, Einsiedel L, Currie BJ 2012; Laupland et al. 2008; Nickerson et al. 2009; Bishara et al. 2012; Bassetti et al. 2011; Turnidge et al. 2009; Kaasch et al. 2014). However, a focus of infection is not found in approximately 25% of cases, and is associated with worse outcomes than lower risk sites, such as intravenous and urinary tract catheters (Van Hal et al. 2012).

SAB can be classified as “complicated” or “uncomplicated”. This designation has important implications for investigations, duration of antibiotic treatment, and overall prognosis. The following criteria are used to define uncomplicated SAB: (i) exclusion of IE by echocardiography, (ii) no implanted prostheses, (iii) negative results of follow-up blood cultures drawn 2 to 4 days after the initial set, (iv) defervescence within 72 h after the initiation of effective antibiotic therapy, and (v) no evidence of metastatic infection (Fowler et al. 2003). Any other patient should be considered to have complicated SAB. Complicated SAB has been shown to occur in over 40% of cases (Fowler et al. 2003). Establishing the status of individual patients with regard to each of these criteria allows appropriate decisions to be made about subsequent treatment duration, which is longer in complicated infections.

The 12-week all-cause mortality ranges between 18 and 30% (Forsblom et al. 2011; Kaasch et al. 2014), varying according to organism-related factors, such as the presence of cloxacillin resistance (Fowler et al. 2003; Wyllie et al. 2006). A lack of improvement in patient outcomes could reflect both a relative decrease in antibiotic efficacy and larger numbers of older, “sicker” patients that now acquire SAB (Tong et al. 2015). Infection-related mortality is estimated at 13% in high income countries (Van Hal et al. 2012).

Predictors of mortality from SAB include increasing age, the presence of co-morbid conditions, the absence of an identifiable source, extent, and persistence of infection, initial inadequate antibiotic treatment, and failure to achieve source control (Turnidge et al. 2009; Bassetti et al. 2011). Several studies have also shown infection with MRSA to be an independent risk factor for mortality in SAB (Cosgrove 2006; Naidoo et al. 2013). Delayed initiation of optimal antibiotic therapy by 2 days has been shown to more than double the risk of mortality (Marchaim et al. 2010; Lodise et al. 2003).

2.6 Management

Both US and UK guidelines for the management of MRSA-bacteraemia (MRSA-B) are available, and recommend a minimum of 2 weeks intravenous therapy for patients with uncomplicated SAB, and longer (4–6 weeks) intravenous antibiotic therapy for those with complicated infections (Liu et al. 2011; Gemmell et al. 2006). Evidence to support various recommendations has been comprehensively reviewed, and is however largely considered to be of a poor quality. Only a single small randomised control trial (RCT) has been performed to examine the optimal duration of antibiotic therapy for any form of SAB (Rahal 1986).

The South African Antibiotic Stewardship Programme (SAASP) has developed an evidence-based antibiotic prescribing guideline, including an algorithm for the treatment of SAB (Wasserman et al. 2014). A minimum of 4 weeks' antibiotic therapy is advised for patients with prosthetic heart valves or endocarditis, persistent bacteraemia or fever after 72 hours of antibiotic therapy, or a non-removable or deep-seated site of infection, such as bone.

The involvement of infectious diseases specialists is an important aspect of management. Recommended management strategies are carried out significantly more frequently among patients seen by an infectious diseases specialist, contributing to the survival benefit (Paulsen et al. 2015; Liu 2013; Vogel et al. 2017).

Administration of appropriate antibiotic therapy has an important influence on the outcomes of both methicillin-sensitive *S. aureus* (MSSA) and MRSA (Van Hal et al. 2012). A meta-analysis of 6 studies demonstrated an almost 2-fold survival benefit (OR, 1.84; 95% CI 1.25 to 2.71) for patients who received appropriate empiric therapy for MRSA-B (Paul et al. 2010).

The treatment of choice for SAB remains cloxacillin or cefazolin (or penicillin if susceptible) for MSSA and vancomycin for MRSA.

One intervention in SAB management that is supported by high quality evidence is early source control, with surgical drainage of collections and removal of intravascular catheters (Thwaites et al. 2017).

Imaging of the cardiac valves is performed in cases of SAB to determine if there is underlying IE present, however it is unresolved whether transoesophageal echocardiography (TOE) is required in all such patients. The SAASP guidelines for SAB recommend echocardiography for the following patients: implanted prosthetic heart valves; clinical evidence of endocarditis; and community-acquired infection, which is associated with an increased risk of complicated SAB. The absence of clinical and microbiological features of complicated SAB have a good negative predictive value (93 to 100%) for endocarditis, and may be used in these settings to identify low risk patients who do not require echocardiography (Holland et al. 2014).

2.7 Studies from South Africa

Only four clinical studies of SAB have been conducted in South Africa, two of which were retrospective in design (Smidt et al. 2015; Naidoo et al. 2013; Perovic et al. 2006; Willcox et al. 1998). A prospective study of 113 consecutive episodes of CA-SAB was conducted at GSH over the years 1986 to 1991 (Willcox et al. 1998). The overall mortality was 35% at 3 months, and complications occurred in 90% of patients, including endocarditis in 17%. A recent prospective study was conducted across three Johannesburg public sector hospitals to describe the epidemiology of MRSA-B and factors associated with poor outcomes (Smidt et al. 2015). The overall proportion of MRSA-B was 36%. The number of patients with complicated SAB was not reported, nor were the overall outcomes and choice and timing of antibiotic therapy.

Because of the paucity of good quality data, the contemporary management and outcomes of SAB in South Africa is not well understood. The proposed study aims to address this knowledge gap by analysing prospectively collected clinical data of consecutive patients with SAB at a referral hospital in Cape Town.

3. Aims and objectives

3.1 Aim

This study aims to improve the recognition and management of SAB by characterising the clinical phenotype in a South African population, as well as exploring the factors associated with poor outcomes.

3.2 Objectives

1. To describe the demographics and clinical characteristics of South African patients with SAB, as well as the microbiological profile of *S. aureus* isolates.
2. To determine the outcomes of patients with SAB at 90 days after the initial blood culture, stratified by CA and HCA, and MRSA and MSSA.
3. To describe the management of SAB, including timing and choice of antibiotic therapy.
4. To explore clinical and microbiological factors associated with complicated SAB and mortality.

4. Methodology

4.1 Definition of terms

Classification of bacteraemia (Friedman et al. 2002):

- Community-acquired: positive blood culture obtained at the time of admission or ≤ 48 hours after admission.
- HCA – hospital onset (HCA-HO): positive blood culture first obtained ≥ 48 hours after admission.
- HCA – community onset (HCA-CO): positive blood culture obtained ≤ 48 hours after admission if the patient (a) had intravenous therapy in the previous 30 days; (b) attended a hospital or received dialysis in the previous 30 days; or (c) resided in a nursing home or long-term care facility.

Source of infection:

- Localising symptoms or signs of infection likely to have preceded bacteraemia.
- Drip site definite: active drip site inflammation in previous 30 days.
- Drip site probable: HCA SAB in a patient with a current or recent (within 30 days) intravenous line and no other clinical focus of infection.

Complicated SAB:

- The presence of 1 or more of the following:
 - Persistent bacteraemia ≥ 72 hours after therapy with an antibiotic to which the isolate has *in vitro* susceptibility
 - Metastatic infection or deep-seated abscess
 - Endocarditis

Cause of death:

- Death was considered to be infection-related if there were persistent signs and symptoms of SAB or if bacteraemia was present at the time of death.

Antibiotic therapy (Asgeirsson et al. 2011; Chang et al. 2003):

- Definitive: antibiotic started after the results of a positive blood culture with *S. aureus* are called out by the microbiology laboratory.
 - Appropriate: use of cloxacillin (at 2 g 6-hourly for uncomplicated infection or 3 g 6-hourly if complicated infection) or penicillin if susceptible for MSSA; or vancomycin (with a loading dose of 25–30 mg/kg followed by 15–20 mg/kg 12-hourly) for MRSA.
 - Semi-appropriate: use of cloxacillin < 12 g/day for complicated SAB.
 - Inappropriate: use of cloxacillin or vancomycin at less than half of standard doses for SAB (or without a loading dose of vancomycin).
- Empiric: antibiotic started at the time of the index blood culture.
 - Adequate: use of optimal therapy or another antibiotic to which the isolate has *in vitro* susceptibility.
 - Inadequate: use of an antibiotic to which the isolate is not susceptible; use of cloxacillin or vancomycin at less than half of standard doses for SAB (or without a loading dose of vancomycin).
- Duration of definitive therapy according to SAASP guidelines
 - Appropriate: ≥ 14 days if no endovascular prosthetic material or endocarditis; resolution of fever and bacteraemia within 72 hours of adequate therapy; and no deep-seated infection (uncomplicated SAB). ≥ 28 days for all other patients (complicated SAB).
 - Semi-appropriate: 10–13 days for uncomplicated SAB; 24–27 days for complicated SAB.
 - Inappropriate: < 10 days for uncomplicated SAB; < 24 days for complicated SAB.
- Overall definitive antibiotic management
 - Optimal: both choice and duration appropriate
 - Suboptimal: either choice or duration semi-appropriate
 - Inadequate: either choice or duration inappropriate

Relapse: A new positive blood culture for *S. aureus* \geq 30 days after a previously sterile blood culture, in a patient who had previously received therapy (any antibiotic or duration) for confirmed SAB.

4.2 Study design

This study is an analysis of a prospective observational study nested within an existing clinical registry in the Division of Infectious Diseases and HIV Medicine (the Division) at Groote Schuur Hospital. The registry and the nested study have prior ethics approval (HREC R004/2012 and HREC 643/2015).

4.3 Setting

The data used for this analysis are from inpatients at GSH, a tertiary referral hospital in the Western Cape province. This hospital serves the Cape metropolitan area, and is the primary teaching hospital associated with the University of Cape Town. GSH also receives direct referrals from clinics within its designated drainage area, and for these patients the hospital serves as a secondary level centre. The hospital includes all major medical and surgical divisions with a total of 893 beds, and has over 40 000 admissions and 21 000 operations per annum. GSH has an on-site diagnostic microbiology laboratory with 3 full-time clinical microbiologists on staff. Results of all significant blood culture isolates (including *S. aureus*) and antibiotic susceptibility data are communicated directly to the requesting physician by phone. All results are also immediately available on the online hospital laboratory results system. However, the finding of gram positive cocci in a positive blood culture is not routinely called out because of high contamination rates with coagulase negative staphylococci.

4.4 Population and sampling

The patient population of GSH is mainly from urban and peri-urban areas, including townships, with a low to middle socio-economic status, and a high burden of HIV and related infections, largely tuberculosis. The clinical details of all inpatient consultations performed by the Division at GSH are recorded in a registry which was set up in 2009, and which currently contains almost 4 000 individual patient records. In November 2013, the Division established a policy that all

patients at GSH with an episode of SAB would be seen by either an infectious diseases specialist or senior registrar. An electronic notification system was set up to facilitate this, whereby the results of all blood cultures positive for *S. aureus* at GSH are automatically sent via email to a member of the Division. The patient is then seen within 36 hours of notification. In addition to this notification, a comment was placed beneath all electronic laboratory reports of SAB episodes detailing the recommended therapy and encouraging referral to Infectious Diseases. This analysis will include the first 100 consecutive distinct SAB infection episodes since the start of the new Divisional policy (November 2013).

Inclusion criteria

- Age > 13 years
- Isolation of *S. aureus* from ≥ 1 blood culture, regardless of clinical evidence of systemic infection (ie. All positive cultures are considered to represent true bacteraemia)
- Single isolate (not mixed with another organism)
- Inpatient at GSH (even if the culture was performed elsewhere)
- A new infection episode is defined as a positive blood culture for *S. aureus* ≥ 30 days after a previously sterile blood culture

4.5 Research procedures and data collection methods

A separate clinical data collection form (in addition to the entry in the general registry) was designed for the purpose of this study (appendix A). Patients with SAB were followed by a member of the Division after the initial consult for the duration of the admission, routinely collected clinical information was entered onto hardcopy data collection forms. 90-day outcome data was obtained using Clinicom, the Provincial digital clinical record system.

The following variables were collected for each patient with SAB and captured on a specifically designed digital spread sheet (Microsoft Excel); the same details are captured in the existing registry:

- **Demographics**
 - Age
 - Sex

- **Medical comorbidities**

- Including specific risk factors for SAB: diabetes, renal disease, alcoholism, HIV infection, presence of active drip-site infection, presence of an endovascular or intra-articular prosthetic material
- Presenting clinical problem
- Clinical evidence of endocarditis: presence of new murmur with or without peripheral immunological or embolic signs

- **Microbiological factors**

- Incubation time
- MSSA or MRSA
- Vancomycin minimum inhibitory concentration (MIC) (for MRSA isolates)
- Antibigram of the isolate
- Time to notification of the clinician by the laboratory (time between initial blood culture and notification)

- **Management**

- Timing of initial blood culture after admission
- Timing and number of repeat blood cultures performed (after empiric and definitive therapy)
- Timing and choice of empiric and definitive therapy
- Dose of vancomycin: use of loading dose; timing and value of trough concentration
- Use of source control (if indicated)
- Use of echocardiography: modality, timing and findings

- **Outcomes**

- Complications of therapy and hospital stay
- Duration of hospital stay
- Relapse
- Mortality: inpatients and 90 days
- Primary cause of death: infection-related or other

4.6 Statistical analysis

Anonymised data captured in Microsoft Excel (2013) spreadsheets will be cleaned and analysed using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.). Descriptive statistics will be used to describe and summarise the data obtained from the study. Normality of data will be assessed using histograms and the Shapiro Wilk test. Kaplan-Meier estimates will be used to describe inpatient survival and time to initiation of antibiotics. Multivariable logistic regression with *a priori* variables identified from the literature will be used to identify factors associated with complicated infection and 90-day mortality. Decisions regarding inclusion of variables in the final model will be based on their effect size on the outcomes of interest. Pictures, graphs, or charts will be used to visually display data. For all statistical tests, a p-value ≤ 0.05 will be considered significant. The specific statistical tests used to address each objective are displayed in Table 1. The data tables used to organise and categorise data are displayed in Tables 2-5.

4.7 Statistical power

From the literature 90-day mortality is hypothesised to be approximately 25% or higher, as a result of the relatively higher HIV prevalence in our sample. With a study population of 100 patients, we will have over 85% power to detect mortality with 95% confidence that is up to 15% higher.

Table 1: Statistical analysis of objectives

Question	Null hypothesis	Statistical test
Objective 1		
What are the demographics, clinical characteristics and microbiological profile of South African patients with SAB?	NA	Descriptive statistics: Categorical variables will be summarized using proportions. If the expected frequencies of all cells in the table are 1 or greater, and no more than 20% of the cells have an expected frequency less than 5, the chi-squared tests will be used to compare proportions. If the assumptions for expected frequencies are not met, the Fischer's exact test will be used. Continuous variables (age) will be assessed for normality using histograms and the Shapiro-Wilk test, and groups compared using t-test if the data are normally distributed, and a paired Wilcoxon signed rank test if not.
Objective 2		
What clinical profile and risk factors of SAB patients are associated with the individual outcomes of both inpatient and 90-day mortality, complicated infection and relapse?	There is no association between HCA vs CA SAB and the resistance pattern of the infecting organism and the individual outcomes of both inpatient and 90-day mortality, complicated infection and relapse.	Descriptive statistics as described above. Survival analysis: Kaplan-Meier estimate and Cox proportional hazards model

Objective 3		
What proportion of SAB patients receive adequate antibiotic therapy, including choice of agent and duration of therapy, comparing MSSA-B and MRSA-B?	There is no association between the resistance profile of the infecting organism and antibiotic management.	Descriptive statistics as described above.
What is the probability of receiving definitive antibiotic therapy by a certain point in time, comparing MSSA-B and MRSA-B?	There is no association between MRSA-B and the time to definitive antibiotic therapy.	Survival analysis: Kaplan-Meier estimate and Cox proportional hazards model
What are the characteristics of patients who underwent echocardiography, and is there a relationship with the diagnostic yield and findings?	There is no association between the presence of clinical endocarditis, prosthetic material and CA-SAB and a positive echocardiography finding.	Descriptive statistics as described above.
Objective 4		
What is the relationship between patient and treatment-related factors and complicated SAB and mortality?	There is no relationship between patient and treatment-related factors and complicated SAB and mortality.	Univariate and multivariate logistic regression analysis. <i>A priori</i> variables: age, sex, cloxacillin resistance, CA vs HCA infection, presence of a comorbidity, adequacy of AB therapy, and time to initiation of definitive therapy. Other variables to be considered: vancomycin MIC and timing to notification of results

Table 2: Data table for objective 1. a) General patient characteristics.

a) General patient characteristics				
	Healthcare-associated (N, %)	Community-associated (N, %)	OR (95% CI)	<i>P</i> -value
Age (years) Mean (\pm SD) >60, no. (%)				
Male, no. (%)				
Co-morbidities HIV positive Diabetes mellitus Renal failure Cardiac disease				
MRSA				
Source of infection Drip site definite Drip site probable SSTI Central line Dialysis catheter Pneumonia Surgical wound UTI Other				
Drip site sepsis				
Metastatic foci				
OR = odds ratio; CI = confidence interval; MRSA = methicillin-resistant <i>staphylococcus aureus</i> ; SSTI = skin and soft-tissue infections; UTI = urinary tract infection.				

Table 3: Data table for objective 2. **a)** Inpatient outcomes, and **b)** 90-day outcomes.

a) Inpatient Outcomes									
		Mortality		Complicated Infection			Relapse	Uncomplicated	Total
		SAB-related	Overall	Persistent	Met Infec/ Abscess	Endo-carditis			
Age	<60								
	≥60								
Sex	Female								
	Male								
Any comorbidities	Yes								
	No								
HIV+	Yes								
	No								
Renal failure	Yes								
	No								
CVS disease	Yes								
	No								
Organism	MSSA								
	MRSA								

b) 90-day Outcomes									
		Mortality		Complicated Infection			Relapse	Uncomplicated	Total
		SAB-related	Overall	Persistent	Met Infec/ Abscess	Endo-carditis			
Age	<60								
	≥60								
Sex	Female								
	Male								
Any comorbidities	Yes								
	No								
HIV+	Yes								
	No								
Renal failure	Yes								
	No								
CVS disease	Yes								
	No								
Organism	MSSA								
	MRSA								

Table 4: Data tables for objective 3. **a)** Adequacy of antibiotic therapy, **b)** Time to definitive antibiotic therapy, and **c)** Echocardiography patient characteristics and findings.

a) Antibiotic therapy				
		Organism		Total
		MSSA	MRSA	
Choice of empiric AB agent	Adequate			
	Inadequate			
Choice of definitive AB agent	Appropriate			
	Inappropriate			
Duration	Appropriate			
	Semi-appropriate			
	Inappropriate			
Overall definitive management	Optimal			
	Suboptimal			
	Inadequate			
b) Time to definitive antibiotic therapy				
		Organism		
		MSSA	MRSA	
N				
Mean				
SD				
P25				
P50				
P75				
IQR				
Min				
Max				
c) Echocardiography				
		Result		Total
		Positive	Negative	
Clinical endocarditis	Yes			
	No			
Prosthetic material	Yes			
	No			
CA vs HCA	CA			
	HCA			

Table 5: Data table for objective 4. **a)** Univariate logistic regression model output, and **b)** Multivariate logistic regression model output.

Covariate	a) Univariate model			b) Multivariate model		
	P-value	Odds Ratio (CI)	R ² (adjusted)	P-value	Odds Ratio (CI)	R ² (adjusted)
Age (ref=<60)						
Any comobidities (ref=no)						
HIV (ref=no)						
Renal failure (ref=no)						
Female sex (ref=male)						
MRSA (ref=MSSA)						
CA (ref=HCA)						
Adequacy of definitive AB therapy (ref=optimal) Suboptimal Inadequate						
Time to initiation of definitive therapy						
Timing to notification of results						
Vancomycin MIC						

5. Ethical considerations

This study aims to abide by the ethical principles of health research that include justice, beneficence, and autonomy. This study will seek ethical approval from University of Cape Town Human Research Ethics Committee (HREC) before proceeding.

Benefits of study

This study aims to describe the management and outcomes of SAB in a local setting, and the information gained through the study may contribute to improving the care of patients with this condition. Individually, participants may have potentially benefitted from inclusion because of more intensive involvement of infectious diseases physicians in their care.

Risks of study

The data collected for this analysis is part of routine patient management, and will therefore have no impact on the clinical care of included subjects. Patient identifiers will only be accessible to the named investigators and will be removed from data entered into the electronic database. Thus, the potential harm for study subjects will be minimal and not clinical in nature, thus adhering to the ethical principle of non-maleficence.

Informed consent process

The analysis makes use of data collected for an existing clinical registry which has been exempted from the requirement of informed consent (HREC R004/2012). Additional data collected especially for this study is included in this exemption.

Privacy and confidentiality

Patient names will not be included in the electronic dataset used for the final analysis. Data from hardcopy extraction sheets will be transferred to and stored in a dedicated, password-protected Excel spreadsheet created specifically for the proposed study. Only the named investigators will have access to this database. Data extraction sheets will be filed and stored in a locked office.

Dissemination of study results

Results of this study will be made available and accessible to researchers in the field of infectious disease by publishing results in the form of a manuscript in a peer-reviewed journal that will be identified. The results of the study will also be made available to the staff at GSH.

6. Study limitations

As the study design is relying on data collected by clinicians during patient care, it relies on the accuracy and completeness of data. The relatively small sample size will limit the statistical power of the study. Additional involvement of ID clinicians in the care of patients with SAB as a part of the study could bias results leading to improved outcomes. This could limit the generalizability of the results to other tertiary hospitals within Sub-Saharan Africa.

7. Study significance

An improved awareness of the management and outcomes of SAB cases in a local South African setting has several potentially significant benefits. The main implication is contributing more knowledge about this disease in our setting, and understanding practice and risk factors that could improve future management. Improved local knowledge about SAB can be useful in predicting prognoses and improving patient outcomes, possibly throughout South Africa.

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Part B. Literature Review

1. Introduction

Staphylococcus aureus is a major human pathogen found worldwide, causing a wide range of clinical infections from skin and soft tissue infections to life-threatening invasive disease. A severe manifestation is *S. aureus* bacteraemia (SAB), a common cause of both community- and hospital-acquired infections. Multiple studies have documented the prevalence and outcomes of SAB in high income countries (HIC), however there remains a paucity of knowledge regarding SAB in low and middle-income countries (LMIC). This information is needed to inform risk stratification and identify areas for improvement in case management. A global concern is also the lack of high-quality evidence to guide the management of SAB.

2. Aims and Objectives

This literature review aims to synthesise and appraise the current literature regarding SAB epidemiology, treatment and outcomes, with the aim to place this research study within context and identify gaps in research.

The specific review objectives are to report the following items and identify needs for further research:

1. The prevalence and clinical burden of SAB
2. Risk factors for acquiring SAB
3. The role of antibiotic-resistant *S. aureus* in SAB
4. Clinical manifestations and outcomes of SAB
5. Management of SAB
6. SAB in LMIC, particularly Sub-Saharan Africa

3. Search Strategy

Literature was sourced using PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>), Google Scholar (<https://scholar.google.co.za/>) and the Cochrane library (<http://www.cochranelibrary.com/>). Medical Subject Heading (MeSH) terms were used to

search Pubmed as a primary source of literature. Google Scholar and the Cochrane Library were use as secondary sources to identify and explore any further articles.

The search terms used across all three databases were similar and focussed on the same themes. The first theme was the epidemiology of SAB, both worldwide and in Sub-Saharan Africa. This included specific mentions of prevalence, risk factors and outcomes. The second theme was the management and treatment of SAB, both worldwide and in Sub-Saharan Africa. The third theme was SAB caused specifically by methicillin-resistant *S. aureus* (MRSA). The specific search terms and strategies are shown in Table 1.

Table 6 Summary of search strategy employed for this literature review

1. PubMed		
<i>Theme</i>	<i>Search terms</i>	<i>Search Strategy</i>
Epidemiology of SAB	<i>Staphylococcus aureus</i> bacteraemia, epidemiology, prevalence, mortality, risk factors and Africa	" <i>Staphylococcus aureus</i> bacteraemia"[MeSH] AND ("epidemiology"[MeSH] OR "prevalence"[All Fields] OR "mortality"[All Fields] OR "risk factors"[All Fields]) AND ("Africa"[MeSH] OR "South Africa"[All Fields] OR "Sub-Saharan Africa"[All Fields] OR "low-income countries"[All Fields] OR "low-middle income countries"[All Fields])
Management of SAB	<i>Staphylococcus aureus</i> bacteraemia and management	("Staphylococcus aureus bacteraemia"[MeSH]) AND ("management"[MeSH] OR "treatment"[All Fields] OR "antibiotics"[MeSH] OR "vancomycin"[All Fields])
Methicillin-resistant <i>S. aureus</i> bacteraemia (MRSA-B)	Methicillin-resistant <i>Staphylococcus aureus</i> bacteraemia	"Methicillin-resistant <i>Staphylococcus aureus</i> bacteraemia"[MeSH] OR "resistant <i>Staphylococcus aureus</i> bacteraemia"[MeSH] OR "MRSA bacteraemia"[All Fields]
2. Google Scholar		
Epidemiology of SAB	<i>Staphylococcus aureus</i> bacteraemia, epidemiology, prevalence, mortality, risk factors and Africa	<i>Staphylococcus aureus</i> bacteraemia AND (epidemiology OR prevalence OR mortality OR risk factors) AND (South Africa OR Africa OR Sub-Saharan Africa OR low-income countries OR low-middle income countries)

Management of SAB	<i>Staphylococcus aureus</i> bacteraemia and management	<i>Staphylococcus aureus</i> bacteraemia AND (management OR treatment OR antibiotics OR vancomycin)
Methicillin-resistant <i>S. aureus</i> bacteraemia (MRSA-B)	Methicillin-resistant <i>Staphylococcus aureus</i> bacteraemia	Methicillin-resistant <i>Staphylococcus aureus</i> bacteraemia
3. Cochrane Library		
Management of SAB	<i>Staphylococcus aureus</i> bacteraemia and management	<i>Staphylococcus aureus</i> bacteraemia and management

3.1 Inclusion criteria

- All published articles written in English. This review was not limited to studies from LMIC as the amount of research from these areas is limited, however papers from Sub-Saharan Africa and other LMICs were given priority, with key papers cited from other regions.
- The measures reported included prevalence, risk factors, complicated infection and mortality.
- Experimental and observational studies were included in this review. More recent studies (published in the past 10 years [2007 to 2017]) were given priority, as were reviews, very large cohorts and multi-centre studies.
- The bibliographies of all the literature that met the inclusion criteria were further examined based on the inclusion criteria used for the initial literature search from in PubMed and Google Scholar.

3.2 Exclusion criteria

- Studies reporting on outcomes within highly specified patient groups e.g. intravenous drug users.

4. Epidemiology

In higher income regions, defined as having a gross national income of \$12 236 or more per capita (World Bank Group 2018), the population incidence of SAB ranges from 10 to 30 per 100 000 person-years, with *S. aureus* being the second most common cause of bloodstream infections (Laupland et al. 2013). Large geographical discrepancies in SAB incidence likely reflect differences in health care systems, infection control practices, and the completeness of surveillance data (Van Hal et al. 2012). Healthcare-associated SAB (HCA-SAB) is associated with higher mortality, longer length of stay, and greater total hospital costs compared to bacteraemia of any other cause in the United States (US) (Shorr et al. 2006).

Far less is known about the incidence and impact of SAB in relatively lower income regions such as Sub-Saharan African. It is likely comparable to high income nations, and may be higher due to the influence of HIV (Larsen et al. 2012). In a systematic review of 22 studies reporting causes of bloodstream infections from more than ten countries on the African continent, the overall prevalence of SAB amongst adult patients admitted with bloodstream infections was 5.4% (111 of 2078 isolates) (Reddy et al. 2010). This study was limited in that hospital-based cohorts were used to describe community-acquired infections, which may have restricted inclusion to those with more severe disease or those who had access to healthcare facilities, resulting in falsely lowered estimates of non-malaria bloodstream infections. Included studies spanned a period of more than 20 years, and therefore acted more as a guide of the range of pathogens causing bloodstream infections, rather than as a reference of current prevalence levels.

A recent cross-sectional study using passive laboratory surveillance of routine clinical cultures from three state hospitals in Gauteng Province, South Africa, showed an SAB incidence of 1.9 to 3.7 cases per 1000 admissions (Smidt et al. 2015). The proportions of healthcare-associated and community-associated SAB were not reported. At Groote Schuur Hospital (GSH), a state hospital in Cape Town, South Africa, an informal review of blood cultures in 2014 showed that over 12 months SAB accounted for 232 of 2 222 (10.4%) positive cultures, and was the second most common pathogen recovered after coagulase-negative staphylococci (Tina Wojno, personal communication). Longitudinal population-based studies are needed to more accurately determine the burden of *S. aureus* in lower income nations.

Table 7 Summary of key studies included on epidemiology of SAB.

Author	Year of publication	Study period	City and country	Study design	Sample size; Median age (IQR)	Aim	Key findings
Larsen et al	2012	1995 - 2007	Denmark	Cohort study	4 871 cases; 92 116 controls	To assess incident rates of SAB in HIV-infected population in era of ART	Among HIV-infected individuals, a latest CD4 count less than 100 cells/mL was the strongest independent predictor of SAB.
Laupland et al	2013	2000 - 2008	Finland, Canberra, Australia, Sweden, Canada, Denmark	Prospective review	18 430; not specified	To define the occurrence of all MSSA and MRSA-bacteraemia within a large multinational population and to evaluate temporal and regional differences	Annual incidence 26.1/100 000 population; incidence rates of hospital-onset MSSA community-onset MRSA and hospital-onset MRSA BSI varied substantially.
Reddy et al	2010	Not specified	≥10 African countries	Systemic review and meta-analysis	58 296; varied	To study the epidemiology of the leading causes of BSI in Africa	531 (9.5%) of non-malarial BSI were due to <i>Staphylococcus aureus</i> .
Shorr et al							
Van Hal et al	2012	Not specified	Mostly high-income countries	Systematic review	Not specified	To review the predictors of mortality in SAB	Incidence rates vary from 19 to 50/100 000 population; age most consistent predictor of mortality.
Note: Studies from South Africa are included in a separate table. ART = antiretroviral therapy; BSI = bloodstream infection; HCA = healthcare-associated; IQR = inter-quartile range; HIV = human immunodeficiency virus; MSSA = methicillin-sensitive <i>S. aureus</i> ; MRSA = methicillin-resistant <i>S. aureus</i> ; SAB = <i>S. aureus</i> bacteraemia; SD = standard deviation.							

5. Risk factors

Various patient factors affect the risk of developing SAB, with the most important of these being the presence of intravascular foreign material, such as peripheral or central intravenous catheters (Jensen et al. 1999; Bassetti et al. 2011), as well as the presence of other prosthetic material, such as joints or heart valves (Forsblom et al. 2011).

Extremes in age have also been shown to be associated with increased SAB incidence. Various studies have shown high rates in the first few years of life, a low incidence in young adulthood, and a gradual rise in incidence with advancing age (Laupland & Church 2014; Allard et al. 2008; Asgeirsson et al. 2011; Huggan et al. 2010). In a South African study, the greatest proportion of SAB occurred in those aged <5 years (Smidt et al. 2015). SAB is also more commonly found amongst males, with a male to female ratio of 3:2 (Allard et al. 2008; Klevens et al. 2007; Asgeirsson et al. 2011; Huggan et al. 2010). However a cohort study in Denmark showed that female patients with community-acquired SAB (CA-SAB) experienced an increased 30-day mortality compared with male patients (Smit et al. 2017), suggesting that sex should be considered in the triage and risk stratification of CA-SAB patients. Ethnicity is also associated with different incidences of SAB, with higher incidences on non-white populations (Klevens et al. 2007; Johnson et al. 2005; Cookson et al. 2012).

People living with HIV (PLWH) have a significantly increased incidence of SAB (Larsen et al. 2012; Wilson et al. 2008). While some of this increase is related to higher rates of intravenous drug use amongst PLWH, SAB incidence is still increased amongst the non-injection drug-using HIV-infected population (Wilson et al. 2008), in whom lower CD4 cell counts have been independently associated with SAB. Men who have sex with men (MSM) have higher rates of HCA-SAB (Wilson et al. 2008). Intravenous drug use is a major risk factor for SAB in all groups, independent of HIV status (Spijkerman et al. 1996; Palepu et al. 2001; Tuazon & Sheagren 1974). In South Africa, HIV infection is associated with a greater incidence of SAB in children (Groome et al. 2012).

Patients receiving haemodialysis are at greater risk of SAB (Kallen et al. 2010; Fitzgerald et al. 2017). The main factor responsible for this increased risk is the presence of an intravascular access device (Fitzgerald et al. 2017). Other host factors amongst dialysis

patients, such as neutrophil dysfunction, iron overload, diabetes, and increased rates of colonisation (Zimakoff et al. 1996), contribute to an impairment in host immunity and thus increase the likelihood of invasive *S. aureus* infections. Dialysis can also affect plasma concentrations of antibiotics, thus potentially decreasing their efficacy and increasing the risk for relapsing SAB (Jeremiah et al. 2014; Vandecasteele & Vriese 2011).

6. Methicillin-resistant *S. aureus*

The development of methicillin resistance in *S. aureus* is associated with increases in mortality, morbidity, length of hospitalisation and cost of health care (Cosgrove 2006). The contribution of MRSA to SAB has varied globally, with recent reductions shown in some high income nations (Johnson et al. 2012; Cookson et al. 2012; Kallen et al. 2010; Jarvie et al. 2008; Jarlier et al. 2010), likely linked to improvements in infection control procedures. MRSA in the US is largely community-acquired and caused by a single clone, USA300. Molecular epidemiology of South African strains suggests that this clone is largely absent, and most MRSA is HCA (Goering et al. 2008). A long-term study in Malawi showed an increase of methicillin resistance in SAB infections from 7.7% of infections in 1998 to 18.4% in 2016 (Musicha et al. 2017). In South Africa, the prevalence of *S. aureus* infections that showed methicillin resistance was approximately 24% between 2007 and 2011 in state sector hospitals (Naidoo et al. 2013; Perovic et al. 2006), and over 30% in private institutions (Brink et al. 2007). In 2015, reported MRSA levels had increased to 36% (Smidt et al. 2015). Approximately 50% of 63 HCA *S. aureus* bloodstream isolates isolated from patients were resistant to cloxacillin at GSH in Cape Town (Mckay & Bamford 2015).

In a recent local study of 365 SAB cases amongst children, MRSA was responsible for 26% of community-acquired SAB and 72% of nosocomial infections (Naidoo et al. 2013). Infants, children with malnutrition, and residents of long-term care facilities were at highest risk for MRSA bacteraemia (Naidoo et al. 2013). The study was retrospective in nature, and may have been biased by non-standardised indications for blood culture, variability in blood culture volumes collected, and the initiation of antibiotics prior to blood culture collection in some cases. One study has shown HIV infection to be a predictor for MRSA infection in the South African setting (Smidt et al. 2015), however 50% of the isolates from one of the

hospitals in the study were not tested for antibiotic susceptibility, which may have biased the results. There was also a large amount of missing data surrounding HIV status and CD4 count.

Table 3 Summary of key studies included on risk factors for SAB.

Author	Year of publication	Study period	City and country	Study design	Sample size; Median age (IQR)	Aim	Key findings
Allard et al	2008	1991-1993 and 2003-2005	Quebec, Canada	Retrospective cohort	324; 66 years (54-75 years)	To examine changes in the incidence and mortality associated with SAB before and after the emergence of MRSA	Incidence of MSSA-B stable, incidence of MRSA-B increased from 0 to 7.4/100 000 population.
Asgeirsson et al	2011	1995-2008	Iceland	Retrospective cohort	692; 63 years	To analyse changes in the incidence and mortality of adult SAB in Iceland	Incidence rose from 22.7 to 28.9 per 100 000 per year during the period.
Bassetti et al	2011	Jan 207 – Dec 2007	Italy	Case control + cohort	171; Not specified	To explore epidemiological characteristics and predisposing risk factors associated with HCA and CA SAB, and to evaluate any differences in mortality and efficacy of initial antimicrobial therapy on treatment outcome	Risk factors for HCA: renal failure, previous hospitalisation or antibiotics. Septic shock, MRSA and inadequate antimicrobial treatment associated with increased mortality.
Cookson et al	2012	2004 - 2008	England, Wales	Prospective study	Not specified	To evaluate the impact of the Cleanyourhands campaign on SAB incidence	Rates fell for MRSA bacteraemia (1.88 to 0.91 cases per 10 000 bed days).
Fitzgerald et al	2017	1998 - 2009	Dublin, Ireland	Retrospective analysis	891; Not specified	To review the changing incidence of SAB in haemodialysis patients	Overall rate of SAB was 17.9 per 100 patient-years. The rate of MRSA - was 5.6 per 100 patient-years.
Forsblom et al	2011	1999-2002	Finland	Prospective cohort	430; Not specified	To compare predisposing factors, disease progression and outcome of HCA- and CA-SAB	54% were HCA. HCA associated with permanent foreign body; deep infection, no infection focus.
Huggan et al	2010	1998-2006	Canterbury, New Zealand	Retrospective analysis	779; 64 years	To describe longitudinal incidence of SAB in a region of New Zealand with low MRSA prevalence	Crude incidence of <i>S. aureus</i> bacteraemia varied between 18.5–27.3/100 000 per annum.
Kallen et al	2010	2005-2008	United States	Prospective surveillance	21 503; not specified	To describe changes in rates of invasive health care-associated MRSA infections from 2005 through 2008 among residents of 9 US metropolitan areas	Incidence of HCA community-onset infections was 2.20 per 10 000 population in 2005 and decreased 5.7% per year.
Wilson et al	2008	200-2004	United States	Retrospective cohort	4 607; not specified	To define the incidence and risk factors for methicillin resistant <i>Staphylococcus aureus</i> (MRSA) bacteraemia in an HIV-infected population	Incidence 19.6 cases per 1000 person-years. Risk factors injection-drug use; renal disease and CD4 <200cells/mL.
Note: studies included in tables from previous sections are not repeated. Studies from South Africa are included in a separate table. HCA = healthcare-associated; IQR = inter-quartile range; HIV = human immunodeficiency virus; MSSA = methicillin-sensitive <i>S. aureus</i> ; MRSA = methicillin-resistant <i>S. aureus</i> ; SAB = <i>S. aureus</i> bacteraemia.							

Part B. Literature review

Table 4 Summary of key studies included on MRSA.

Author	Year of publication	Study period	City and country	Study design	Sample size; Median age (IQR)	Aim	Key findings
Goering et al	2008	2004-2005	United States, Peru, South Africa, India, Germany, Russia	Prospective molecular analysis	292; not specified	To determine the genetic characteristics of <i>Staphylococcus aureus</i>	The most common MRSA clone had sequence type 8: USA300. This clone was isolated exclusively in the United States and is CA.
Mckay et al	2015	October 2011-September 2012	Cape Town, South Africa	Retrospective review	740; not specified	To describe the distribution of organisms and of antibiotic susceptibility among isolates from blood cultures at a tertiary academic hospital, stratifying by place of infection acquisition.	Nearly three-quarters of infections were healthcare acquired. All CA SAB isolates v. 52.4% of HCA isolates were susceptible to cloxacillin.
Jarlier et al	2010	1993-2007	Paris, France	Prospective observational	NA	To determine the effect of a long-term infection prevention initiative on MRSA rates	There was a significant progressive decrease in MRSA burden (–35%) from 1993 to 2007.
Kallen et al	2010	2005-2008	United States	Prospective observational	21 503, not specified	To describe changes in rates of invasive health care–associated MRSA infections from 2005 through 2008 among residents of 9 US metropolitan areas	The incidence rate of hospital-onset invasive MRSA infections was 1.02 per 10 000 population in 2005 and decreased 9.4% per year.
Musicha et al	2017	1998-2016	Malawi	Surveillance study	29 183	To report long-term trends in bloodstream infection and antimicrobial resistance	MRSA was first reported in 1998 at 7.7% and represented 18.4% of <i>S. aureus</i> isolates in 2016.
Note: studies included in tables from previous sections are not repeated. Studies from South Africa are included in a separate table. HCA = healthcare-associated; IQR = inter-quartile range; MSSA = methicillin-sensitive <i>S. aureus</i> ; MRSA = methicillin-resistant <i>S. aureus</i> ; SAB = <i>S. aureus</i> bacteraemia.							

7. Clinical manifestations and outcomes

The presence of various primary clinical foci for SAB may be identified, with common sources being vascular catheter-related infections, skin and soft tissue infections, pleuropulmonary infections, osteoarticular infections and infective endocarditis (IE) (Laupland et al. 2008; Bishara et al. 2012; Bassetti et al. 2011; Turnidge et al. 2009; Kaasch et al. 2014; Van Hal et al. 2012). In many cases a source of infection is not found, and is associated with worse outcomes than infection sources such as intravenous and urinary tract catheters (Van Hal et al. 2012).

SAB can be classified as “complicated” or “uncomplicated”. This designation has important implications for investigations, duration of antibiotic treatment, and overall prognosis. A key The following criteria have been used to define uncomplicated SAB: (i) exclusion of IE by echocardiography, (ii) no implanted prostheses, (iii) negative results of follow-up blood cultures drawn 2 to 4 days after the initial set, (iv) defervescence within 72 hours (h) after the initiation of effective antibiotic therapy, and (v) no evidence of metastatic infection (Fowler et al. 2003). Any other patient should be considered to have complicated SAB. In a prospective, observational cohort study of 724 patients with SAB in the US, complicated infection was present in over 40% of cases (Fowler et al. 2003). Establishing the status of individual patients regarding each of these criteria allows appropriate decisions to be made about subsequent treatment duration. Failure of identification of complications can lead to relapsing bacteraemia and poor outcomes (Fowler et al. 2003).

A pooled analysis of 3 395 adult patients with SAB in centres in Germany, Spain, the UK and the US showed a crude 90-day mortality of 29.2% (Kaasch et al. 2014), increased in cases of HCA and MRSA infection. However only tertiary care patients were included, and limited data were available describing disease comorbidities and disease severity at SAB onset. A UK study of 724 adult patients reported a mortality of 29.0%, varying according to organism-related factors, such as the presence of cloxacillin resistance (Fowler et al. 2003). A lack of improvement in patient outcomes could reflect both a relative decrease in antibiotic efficacy and larger numbers of older, “sicker” patients that now acquire SAB (Tong et al. 2015). Infection-related mortality is estimated at 13% in high income countries (Van Hal et al. 2012).

Predictors of mortality from SAB include increasing age, the presence of co-morbid conditions, the absence of an identifiable source, extent, and persistence of infection, initial inadequate antibiotic treatment, and failure to achieve source control (Bassetti et al., 2011; Braquet et al., 2016; Turnidge et al., 2009). Several studies have also shown infection with MRSA to be an independent risk factor for mortality in SAB (Cosgrove 2006; Naidoo et al. 2013). Delayed initiation of optimal antibiotic therapy by two days has been shown to more than double the risk of mortality (Marchaim et al. 2010; Lodise et al. 2003).

While HIV is associated with an increased risk of HIV acquisition, its effect on mortality remains uncertain. Several studies have reported no increase in mortality (Perovic et al., 2006; Senthilkumar et al., 2001). A more recent case-control study in Denmark showed an increased 30-day mortality rate (OR 11.9; 95% 2.2 to 65.9) in PLWH (Jaliff et al., 2014), however the retrospective design and small sample size of this study may have limited its validity, and HIV-related factors such as CD4 count, antiretroviral therapy and viral load were not associated with increased mortality. This may suggest that it is increased interaction with healthcare services and subsequent exposure to *S. aureus* via venous cannulation, resulting in increased rates of re-infection, which may be contributing more to the increased mortality rather than HIV infection itself.

Author	Year of publication	Study period	City and country	Study design	Sample size; Median age (IQR)	Aim	Key findings
Bishara et al	2012	1988-2007	Petah Tikva, Israel	Retrospective cohort	1347; not specified	To analyse clinical features and outcomes of patients with HCA SAB.	Mortality at 30 days was 40.2% (507/1261) and at 1 year was 63.4% (800/1261).
Braquet et al	2016	2009-2011	France	Prospective cohort	2091; 67.8 years (55.5-78.9 years)	To identify prognostic factors in a large prospective cohort of SAB patients and to analyse the impact of first-line anti-biotics on case-fatality.	Week 12 case-fatality rate was 671/1972 (34.0%). Main prognostic factors: age, septic shock, unknown primary focus, metastatic cancer. Initiating empiric antibiotics with antistaphylococcal penicillins or vancomycin may be associated with better outcome in MSSA bacteraemia.
Fowler et al	2003	1994-1999	Durham, England	Prospective cohort	724; 58.5 years (SD 16.2)	To define readily available clinical characteristics that could help identify patients at risk for complicated SAB.	Complicated SAB was present in 43% of 724 consecutive adult hospitalized patients. A scoring system based on the presence or absence of 4 risk accurately identified complicated SAB.
Kaasch et al	2014	2006-2011	Germany, Spain, United Kingdom, United States	Prospective cohort	3395; 64 years (50-75 years)	To describe how its clinical presentation varies between populations and to identify common determinants of outcome.	Crude 14 and 90-day mortality was 14.6% and 29.2%, respectively. Age, MRSA bacteraemia, nosocomial acquisition, endocarditis, and pneumonia were independently associated with death, but a strong association was with an unidentified infective focus.
Laupland et al	2008	200-2006	Calgary, Canada	Prospective cohort	1508; not specified	To describe the epidemiological profile of SAB	Case fatality rate higher in MRSA (39%) than MSSA (24%, $p < 0.0001$)
Lodise et al	2003	1999-2001	Michigan, United States	Retrospective cohort analysis	458; 54.2 years (SD 16.6 years)	to determine the effect of delayed therapy on morbidity and mortality associated with nosocomial SAB	Delayed treatment is independent predictor of infection-related mortality (odds ratio, 3.8; 95% confidence interval, 1.3–11.0; $p = 0.01$)
Marchaim et al	2010	2001-2005	United States	Case-control	388; 69.1 years (SD 17.8 years)	To determine association of risk factors with SAB mortality	Delayed appropriate antibiotic therapy was significantly associated with increased mortality ($p = 0.04$)
Tong et al	2015	Not specified	High and low income countries	Systematic review	Not specified	To describe the epidemiology, pathophysiology, clinical manifestations, and management of <i>S. aureus</i> infections.	Predictors of mortality include: age, co-morbidities, source and extent of infection.
Turnidge et al	2009	2007-2008	Australia, New Zealand	Prospective cohort	1994; not specified	To document the types of, and mortality from, SAB in Australia and New Zealand, and determine factors associated with mortality	Independent predictors of mortality were age, sepsis syndrome, pneumonia, a secondary focus, endocarditis.
Note: studies included in tables from previous sections are not repeated. Studies from South Africa are included in a separate table. HCA = healthcare-associated; IQR = inter-quartile range; MSSA = methicillin-sensitive <i>S. aureus</i> ; MRSA = methicillin-resistant <i>S. aureus</i> ; SAB = <i>S. aureus</i> bacteraemia; SD = standard deviation.							

Table 5 Summary of key studies included on SAB outcomes.

8. Management

Both US and United Kingdom guidelines for the management of MRSA-bacteraemia (MRSA-B) are available, and recommend a minimum of 2 weeks intravenous therapy for patients with uncomplicated SAB, and longer-term (4–6 weeks) intravenous antibiotic therapy for those with complicated infections (Liu et al. 2011; Gemmell et al. 2006). Evidence to support various recommendations is largely considered to be of a poor quality. Only a single small randomised control trial (RCT) has been performed to examine the optimal duration of antibiotic therapy for any form of SAB, and reported insufficient data to allow conclusions regarding the optimal duration of therapy for patients with or without endocarditis (Rahal 1986).

The South African Antibiotic Stewardship Programme (SAASP) has developed an antibiotic prescribing guideline based on currently available evidence, including an algorithm for the treatment of SAB (Wasserman et al. 2014). A minimum of 4 weeks antibiotic therapy is advised for patients with prosthetic heart valves or endocarditis, persistent bacteraemia or fever after 72 h of antibiotic therapy, or a non-removable or deep-seated site of infection, such as bone.

The involvement of infectious diseases (ID) specialists is an important aspect of management. Recommended management strategies are carried out significantly more frequently among patients seen by an infectious diseases specialist, contributing to the survival benefit (Paulsen et al. 2015; Liu 2013; Vogel et al. 2016). A systematic review and meta-analysis of 18 reports showed a significant reduction in 30-day mortality in SAB patients seen by an ID consultant compared with those who did not have an ID consult (Vogel et al. 2016), with a relative risk of 0.53 (95% CI 0.43-0.65). Follow-up blood cultures and echocardiography were also performed more frequently following ID consultation. Possible selection bias was present, as ID consultation was most likely selected for more severe disease and poorer prognosis, which decreased the likelihood of finding a positive effect. This bias was minimised by adjusting for patient and SAB baseline characteristics using multivariable modelling and propensity score matching. Potential confounding may also have been present in the fact that patients with better resources and those cared for in better resourced health facilities were more likely to see an ID specialist, thus biasing towards better outcomes. This was addressed using case matching within healthcare facilities.

Administration of appropriate antibiotic therapy has an important influence on the outcomes of both methicillin-sensitive *S. aureus* (MSSA) and MRSA (Van Hal et al. 2012). A meta-analysis of 6 studies demonstrated an almost two-fold survival benefit (OR, 1.84; 95% CI 1.25 to 2.71) for patients who received appropriate empiric therapy for MRSA-B (Paul et al. 2010). In a cohort study of 1 896 patients with MSSA-bacteraemia (MSSA-B), first-line empiric antistaphylococcal penicillins (OR, 0.40; CI, 0.17-0.95) and vancomycin (OR, 0.37; CI, 0.17-0.83), alone or combined with an aminoglycoside, were associated with improved mortality compared to other antibiotics (Braquet et al. 2016). Sterilisation of blood is achieved more rapidly with the use of beta-lactam drugs compared with vancomycin for MSSA-B (Khatib et al. 2009; Siegman-igra et al. 2005). There is also evidence that the use of vancomycin for SAB, regardless of beta lactam susceptibility, is an independent risk factor for recurrence and death (Mcconeghy et al. 2013; Johnson et al. 2003; Chang et al. 2003). Cephalosporins are frequently used for empiric therapy for hospitalised patients, but no comparative RCTs have been performed to evaluate the efficacy of cephalosporins for the treatment of MSSA-B. Limited observational data have shown favourable outcomes for cefazolin, but concerns exist about treatment failure in complicated SAB, particularly with the use of second and third generation cephalosporins (Thwaites et al. 2017). Another agent shown to have similar efficacy to standard therapy for both MSSA and MRSA bacteraemia in an RCT is the lipopeptide daptomycin (Fowler et al. 2006); however this drug is not available in the public sector in South Africa. Thus, the treatment of choice for SAB remains cloxacillin (or penicillin if susceptible) for MSSA and vancomycin for MRSA.

One intervention in SAB management that is supported by high quality evidence is early source control, with surgical drainage of collections and removal of intravascular catheters (Thwaites et al. 2017).

Imaging of the cardiac valves is performed in cases of SAB to determine if there is underlying IE present, however it is unresolved whether transoesophageal echocardiography (TOE) is required in all patients. The SAASP guidelines for SAB recommend echocardiography for the following patients: implanted prosthetic heart valves; clinical evidence of endocarditis; and community-acquired infection, which is associated with an increased risk of complicated SAB. TOE has an increased sensitivity for the detection of IE when compared to transthoracic echocardiography (TTE), however it is more expensive, less widely available, and is an invasive

procedure (Fowler et al. 1997; Hal et al. 2005; Khatib & Sharma 2013). The absence of clinical and microbiological features of complicated SAB have a good negative predictive value (93 to 100%) for endocarditis, and may be used in these settings to identify low risk patients who do not require echocardiography (Holland et al. 2014).

Table 6 Summary of key studies on management of SAB.

Author	Year of publication	Study period	City and country	Study design	Sample size; Median age (IQR)	Aim	Key findings
Fowler et al	1997	1994-1996	United States	Prospective cohort	103; 56 years (SD 15 years)	To examine the role of echocardiography in patients with SAB.	IE is common among patients admitted to the hospital with SAB and is associated with an increased risk of death due to sepsis.
Holland et al	2014	1990-2014	Not specified	Systematic review	4050, not specified	To review evidence of management strategies for SAB	All adult patients with SAB should undergo echocardiography, unless identified with low-risk characteristics. Vancomycin and daptomycin are the first-line choices for MRSA-B.
Paulsen et al	2015	Not specified	22 studies	Systematic review	Not specified	To assess whether consultation with infectious disease specialists decreased all-cause mortality or rate of complications of SAB	Recommended management strategies were carried out significantly more often among patients seen by an infectious disease specialist.
Rahal	1986	Unable to access	Unable to access	Randomised control trial	84; not specified	To determine the role of antimicrobial therapy on SAB outcome.	Data were insufficient to allow conclusions regarding the optimal duration of therapy for patients with or without endocarditis.
Thwaites et al	2017	Not specified	High income countries	Systematic review	Not specified	To describe the key principles for SAB management	Early source control and long-term antimicrobial treatment for complicated infection are key.
Vogel et al	2016	Inception to May 2015	Not specified	Systematic review and meta-analysis	5 377; not specified	To evaluate the impact of infectious disease consultation on the management and outcomes of patients with SAB	The appropriateness of antistaphylococcal agent and treatment duration was improved by infectious disease consultation; mortality was decreased; follow-up blood cultures and echocardiography performed more frequently.
Note: studies included in tables from previous sections are not repeated. Studies from South Africa are included in a separate table. IQR = inter-quartile range; MRSA = methicillin-resistant <i>S. aureus</i> ; SAB = <i>S. aureus</i> bacteraemia; SD = standard deviation.							

9. Studies from South Africa

Only five clinical studies of SAB have been conducted in South Africa (Table 2), three of which were retrospective in design and two of which focussed exclusively on children (Smidt et al. 2015; Naidoo et al. 2013; Perovic et al. 2006; Willcox et al. 1998; Groome et al. 2012). A prospective study of 113 consecutive episodes of CA-SAB was conducted at GSH over the years 1986 to 1991 (Willcox et al. 1998). Eleven percent of isolates were resistant to cloxacillin, and none of the patients were HIV-infected. The overall mortality was 35% at 3 months, and complications occurred in 90% of patients, including endocarditis in 17%. Treatment was delayed by 24 h or more in 50% of all patients, and significantly more patients who died had received either inadequate or no antibiotic therapy compared to survivors.

A recent prospective study was conducted across three Johannesburg public sector hospitals to describe the epidemiology of MRSA-B and factors associated with poor outcomes (Smidt et al. 2015). For unreported reasons, only 45% of all SAB episodes in the study period were included in the analysis, with a final study size of 240 isolates. The overall proportion of MRSA-B was 36%. The number of patients with complicated SAB was not reported, nor were the overall outcomes and choice and timing of antibiotic therapy.

A retrospective review of SAB cases at two academic hospitals in Johannesburg, South Africa, reported on 449 episodes of SAB between 1999 and 2002 (Perovic et al. 2006). HCA infection was associated with an increased risk of MRSA-B. Intensive care unit admission and MRSA infection were strongly associated with increased mortality. Only 14-day mortality was studied, and antibiotic management was not assessed.

A retrospective review of 161 cases of SAB in children hospitalised between 2005 and 2006 at a tertiary state hospital in Johannesburg, South Africa (Groome et al. 2012), reported an incidence of 26 per 100 000 population per year, with 63 (39%) isolates identified as methicillin-resistant. Incidence was inversely related to age and greater in PLWH. Overall mortality was not reported. The retrospective design of the study, as well as the fact that children admitted to private hospitals or who had died in the community before seeking healthcare were not included, limited the accuracy of true SAB incidence. If the HIV status of

the child was unknown, they were assumed to be HIV negative, which may have resulted in misclassification bias.

A separate retrospective study in children was carried out between 2007 and 2011 at a children's hospital in Cape Town, South Africa (Naidoo et al. 2013). Over the study period, 365 cases of SAB were identified, with an annual incidence of 3.28 cases per 1 000 hospital admissions. The overall case fatality rate was 8.8% over five years, with only MRSA infection identified as a significant risk factor for mortality. MRSA was responsible for 26% of SAB and 72% of nosocomial infections. Again, this study is limited by its retrospective nature, resulting in a lack of standardisation of blood culture investigations and treatment protocols.

10. Conclusion

The predisposing factors and patient characteristics of SAB are well-described in HIC, however relatively little is known about SAB in the Southern African setting. Despite being a leading cause of bloodstream infections, there is a lack of quality evidence to guide the management of SAB. Previous studies have lacked standardisation and did not thoroughly evaluate treatment strategies. Because of the paucity of good quality data, the contemporary management and outcomes of SAB in South Africa is not well understood. The proposed study aims to address this knowledge gap by analysing prospectively collected clinical data of consecutive patients with SAB at a referral hospital in Cape Town, with the objectives of describing the South African patient profile of SAB, the antibiotic management, and the clinical and microbiological factors associated with poor outcome.

Author	Year of publication	Study period	City and country	Study design	Sample size; Median age (IQR)	Aim	Key findings
Groom et al	2012	January 2005 - December 2006	Johannesburg, South Africa	Retrospective record review	161; 7.5 months (3 days – 12.5 years)	To describe the burden of community-onset bacteraemic <i>S. aureus</i> infections in children in an area with a high prevalence of paediatric HIV infection, and to describe the antimicrobial resistance patterns.	Incidence 26/100 000; MRSA 39% overall; increased incidence in HIV infection.
Naidoo et al	2013	2007 - 2011	Cape Town, South Africa	Retrospective analysis	365; 11.3 months (3.8 – 42.3 months)	To investigate the epidemiology of SAB at a single children's hospital in South Africa over a five-year period, and to describe the incidence, clinical presentation, microbiologic profiles, risk factors, management and outcomes of children with both MSSA and MRSA bacteraemia.	Incidence 3.28/1000 hospital admissions; MRSA 26% overall and 72% of nosocomial infections; overall case fatality rate 8.8% over 5 years, with MRSA being the only significant risk factor for mortality.
Perovic et al	2006	November 1999 – October 2002	Johannesburg, South Africa	Retrospective analysis	449; 41.6 years (SD 15.8 years)	To determine the number of patients presenting with SAB, to determine the proportion of MRSA versus MSSA infections, to determine the mortality rate of patients with SAB, to compare the mortality rate of MRSA versus MSSA SAB, and to identify risk factors associated with mortality.	14-day mortality rate 23.2%; MRSA 23.4% overall, MRSA infection associated with HCA infection and increased mortality intensive care unit admission associated with increased mortality.
Smidt et al	2015	September 2012 – September 2013	Johannesburg, South Africa	Prospective review	442; 29 years (0.4 – 45 years)	To describe the epidemiology of <i>S. aureus</i> bacteraemia and to determine factors associated with MRSA infection in South Africa.	MRSA 36% overall; MRSA infection associated with recent hospitalisation, HIV infection and recent antibiotic use; increased age associated with increased mortality.
Willcox et al	1998	February 1986 - January 1991	Cape Town, South Africa	Prospective review	113; 46 years (IQR not reported)	To describe community-acquired <i>S. aureus</i> bacteraemia in a population where intravenous drug abuse is extremely uncommon.	Mortality 35%; acute renal failure, shock and confusion associated with increased mortality; unknown infection focus in 58%.
HCA = healthcare-associated; IQR = inter-quartile range; MSSA = methicillin-sensitive <i>S. aureus</i> ; MRSA = methicillin-resistant <i>S. aureus</i> ; SAB = <i>S. aureus</i> bacteraemia; SD = standard deviation.							

Table 7 Summary of studies on SAB from South Africa.

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Part C. Journal Manuscript¹

¹ This manuscript follows the author instructions for the *International Journal of Infectious Disease*. These instructions are detailed in the Appendix C. For readability, figures and tables are inserted in the text of the dissertation, rather than appended at the end of the article. The referencing style (used throughout this dissertation) is as required by the *International Journal of Infectious Disease*.

The Management and Outcomes of *Staphylococcus aureus* Bacteraemia at a South African Referral Hospital: A Prospective Observational Study²

ABSTRACT

Objectives Limited evidence exists on the management and outcomes of *Staphylococcus aureus* bacteraemia (SAB) in resource-limited settings. The aim of this study was to describe a cohort of South African patients with SAB, and explore the factors associated with complicated infection and death.

Method A prospective observational study of patients over the age of 13 years admitted to a South African referral hospital with SAB.

Results One hundred SAB infection episodes occurring in 98 patients were included. SAB was healthcare-associated in 68.4%; 24.0% of all cases were caused by methicillin-resistant *S. aureus* (MRSA). Ninety-day mortality was 47.0%, with 83.3% of deaths attributable to SAB. There was a trend towards increased 90-day mortality with MRSA infection (OR 1.28; 95% CI 1.0 to 15.1) and the presence of co-morbidities (OR 4.1; 95% CI 1.0 to 21.6). The risk of complicated infection was higher with non-optimal definitive antibiotic therapy (OR 8.5; 95% CI 1.8 to 52.4), female sex (OR 3.8; 95% CI 1.1 to 16.3) and community-acquired infection (OR 7.4; 95% CI 2.0 to 33.1). Definitive antibiotic therapy was non-optimal in 22.6% of all cases.

Conclusions SAB-related mortality was high. A large proportion of cases may be preventable, and there is a need for improved antibiotic management.

[Word count: 200]

Keywords

Staphylococcus aureus bacteraemia; methicillin-resistant *Staphylococcus aureus*; antibiotic stewardship

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INTRODUCTION

Staphylococcus aureus is a major human global pathogen, causing a wide range of infections. *S. aureus* bacteraemia (SAB) is an especially severe manifestation, and a common cause of community- and hospital-acquired bacteraemia in high-income countries with a population incidence of 10 to 30 per 100 000 person-years (Laupland et al., 2013). A number of clinical predictors of mortality have been identified in these settings, but there is limited knowledge regarding optimal antibiotic management (Rahal, 1986), and outcomes remain poor (Forsblom et al., 2011; Holland, Arnold, & Fowler, 2014; Kaasch et al., 2014). Less is known about the incidence and impact of SAB in low- and middle-income countries (LMICs). The burden is likely comparable to high income nations (Reddy, Shaw, & Crump, 2010), and may be higher due to the influence of HIV infection (Larsen et al., 2012) and differences in health care systems and infection control practices (Van Hal et al., 2012).

Three previous clinical studies of SAB amongst adult patients have been conducted in South Africa, two of which were retrospective (Perovic et al., 2006; Smidt et al., 2015; Willcox, Rayner, & Whitelaw, 1998). In the most recent study, the number of patients with complicated SAB was not reported, nor were the overall outcomes or choice and timing of antibiotic therapy (Smidt et al., 2015). Because of the paucity of good quality data, the contemporary management and outcomes of SAB in South Africa are not well understood. We conducted a prospective observational study to describe a cohort of patients with SAB, assess outcomes, and explore the factors associated with complications and death at a South African referral hospital.

PATIENTS AND METHODS

Study setting and population

Participants in this study were recruited at Groote Schuur Hospital, a large academic referral center in Cape Town, South Africa. The patient population is mainly from urban and peri-urban areas, including townships, with a low to middle socio-economic status, and a high burden of HIV and related infections, largely tuberculosis.

Inclusion criteria and data collection

In 2013, the Division of Infectious Diseases and HIV Medicine at Groote Schuur Hospital initiated a policy to review all new cases of SAB in the hospital. Cases are identified using an electronic laboratory notification system whereby the results of all blood cultures positive for *S. aureus* are automatically sent via email to a member of the Division of Infectious Diseases and underwent clinical assessment within 36 hours of notification. This analysis includes the first 100 consecutive SAB infection episodes assessed since the start of the policy. Inclusion criteria were inpatients at Groote Schuur Hospital over 13 years of age, with a pure growth of *S. aureus* in one or more blood cultures.

Enrolled participants were followed up for the duration of their admission. Routinely collected clinical information was entered onto hardcopy case report forms. This included data on demographics, medical comorbidities, clinical profile, timing of blood cultures, timing and choice of antibiotic therapy, duration of hospital stay and inpatient mortality. The requirement for informed consent was waived by the ethics review committee as data were collected as part of an ongoing approved clinical registry. Vital status at 90-days was ascertained from Clinicom, the Provincial digital record and appointment system. Microbiological data were obtained from the National Health Laboratory Service (NHLS) data warehouse, and included antibiotic susceptibility profiles, the vancomycin minimum inhibitory concentration (MIC) for MRSA isolates, and time to notification of blood culture results to treating physicians.

Definitions

A new infection episode was defined as a positive blood culture for *S. aureus* \geq 30 days after a previously sterile blood culture. SAB was classified as community-acquired (CA-SAB) if a positive blood culture for *S. aureus* was first obtained at the time of admission or within 48 hours of admission. Bacteraemia was classified as healthcare-associated (HCA-SAB) if a positive blood culture was first obtained more than 48 hours after admission, or if the first positive blood culture was within 48 hours of admission but the patient had (i) received intravenous therapy in the previous 30 days; (ii) attended a hospital or received dialysis in the previous 30 days; or (iii) resided in a nursing home or long-term care facility.

Complicated SAB was defined by the presence of one or more of the following: (i) persistent bacteraemia \geq 72 hours after therapy with an antibiotic to which the isolate had *in vitro* susceptibility; (ii) metastatic infection or deep-seated abscess, or (iii) endocarditis

(Corey, 2009). Death was considered to be infection-related if there were persistent signs and symptoms of SAB or if bacteraemia was present in the last culture prior to death.

Antibiotic prescriptions were designated 'definitive' once treating physicians were notified of a positive blood culture for *S. aureus*. Optimal choice and administration of definitive antibiotic therapy for methicillin-sensitive *S. aureus* (MSSA) was defined as the use of intravenous cloxacillin 2g 6-hourly in uncomplicated infection, or 3g 6-hourly if complicated infection (or guideline-recommended alternatives). For MRSA, optimal therapy included a loading dose of vancomycin at 25-35mg/kg, followed by 15-20mg/kg 12-hourly. Duration of antibiotic therapy was classified according to local (Wasserman, Boyles, & Mendelson, 2014) and international (Liu et al., 2011) guidelines and best practice (Thwaites et al., 2017). Optimal duration was ≥ 14 days for uncomplicated SAB or ≥ 28 days for complicated SAB (Thwaites et al., 2017). Overall definitive antibiotic management was designated as non-optimal if either administration or duration was outside of these guidelines.

Empiric therapy was defined as an antibiotic administered at the time of the index blood culture, prior to the notification of the presence of SAB. This was classified as inadequate in the following situations: the use of an antibiotic to which the isolate is not susceptible or use of cloxacillin or vancomycin at less than half of standard doses for SAB (or without a loading dose of vancomycin).

Statistical analysis

Data captured in Microsoft Excel (2013) were analysed using R (R Core Team, 2016). Descriptive statistics were used to summarize the data, stratified by HCA/CA. Multivariable logistic regression with *a priori* variables identified from the literature was used to identify factors associated with complicated infection and 90-day mortality. Variables selected for inclusion in the final model were age (Forsblom et al., 2011), sex (Smit et al., 2017), MRSA (Cosgrove, 2006; Naidoo et al., 2013), healthcare-associated infection (Fowler et al., 2003), presence of comorbidities (Fitzgerald et al., 2017; Larsen et al., 2012), and time to definitive antibiotic therapy (Lodise, Mckinnon, Swiderski, & Rybak, 2003; Marchaim et al., 2010); these were included based on their effect size on the outcomes of interest. Model selection was performed using the Akaike Information Criterion (AIC). We used Kaplan-Meier estimates for inpatient survival and time to initiation of antibiotics. For all statistical tests, a p-value ≤ 0.05 was considered significant.

Ethics approval

This study was approved by the Human Research Ethics Committee at the University of Cape Town (Ref: 643/2015).

RESULTS

Patient and infection characteristics

One hundred consecutive, distinct SAB infection episodes in 98 patients were identified between November 2013 and January 2015. Baseline characteristics, stratified by place of acquisition of infection are shown in Table 1. Median time to notification to the treating physician of confirmed *S. aureus* blood culture results was 44 hours (interquartile range (IQR) 37 to 53) from the time the blood culture was taken. SAB was healthcare-associated in 67 (68.4%, $n = 98$) cases of infection, with 57 (85.1%, $n = 67$) of these linked to intravenous catheter-site infection. MRSA accounted for 23.5% of all infections, of which 82.6% were health-care associated. Minimum inhibitory concentrations of vancomycin for MRSA strains ranged from 0.5 $\mu\text{g/ml}$ to 2 $\mu\text{g/ml}$, with 4 (19.0%, $n = 21$) having a MIC > 1 $\mu\text{g/ml}$. Full antibiotic susceptibility profiles are shown in Figure 1. There were no significant univariate predictors for infection with MRSA (data not shown).

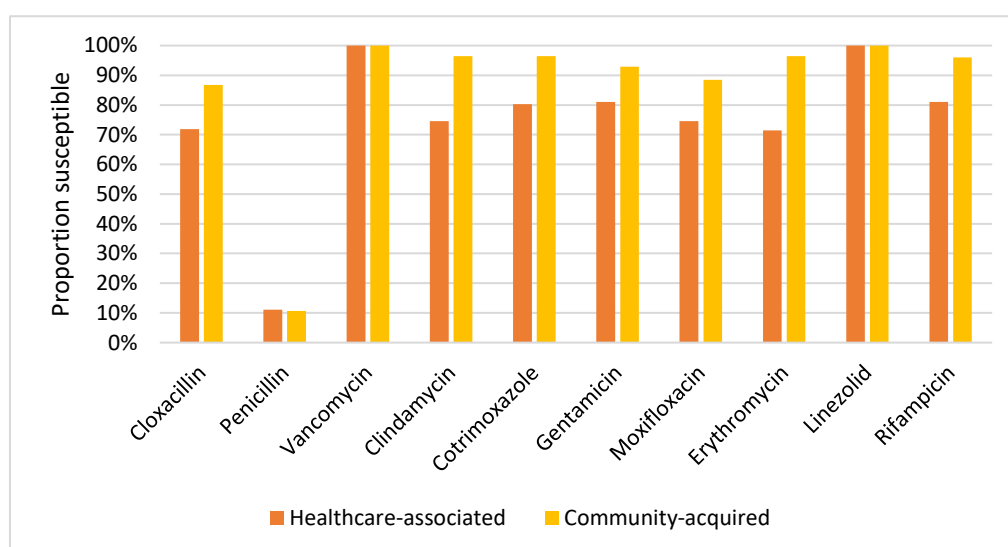


Figure 1 Antibiotic susceptibility profiles of *S. aureus* isolates.

Table 8 Patient and infection characteristics.

	Healthcare-associated (N = 67)	Community-acquired (N = 31)	Total (N = 100)
Age, years	48.3 ± 18.4	49.1 ± 18.6	
Age > 60 years	17 (25)	10 (32)	27 (28)
Male sex	43 (64)	27 (87)*	70 (71)
Co-morbidities (any)	55 (85)	23 (74)	78 (81)
HIV positive	14 (26)	3 (12)	17 (22)
Diabetes mellitus	11 (17)	8 (26)	19 (20)
Renal failure	22 (33)	8 (26)	30 (31)
Cardiac disease	18 (28)	11 (36)	29 (30)
MRSA	19 (28)	4 (13)	23 (24)
Source of infection			
Drip site definite	12 (20)	NA	12 (16)
Drip site probable	22 (37)	NA	22 (29)
SSTI	5 (9)	11 (65)	16 (21)
Central line	4 (7)	NA	4 (5)
Dialysis catheter	5 (9)	NA	5 (7)
Pneumonia	3 (5)	2 (12)	5 (7)
Surgical wound	4 (7)	1 (6)	5 (7)
UTI	2 (3)	2 (12)	4 (5)
Other	2 (3)	1 (6)	3 (4)
Drip site sepsis	19 (29)	NA	19 (20)
Metastatic foci	12 (19)	15 (50)*	27 (28)
Data are n (%) and mean (SD). Percentages given have a denominator of N as shown in the column heading. *No characteristic differed significantly between the study groups ($P \leq 0.05$ at baseline according to Fisher's exact test for categorical data or the Wilcoxon rank-sum test for continuous data), with the exception of male sex ($P = 0.0195$) and the presence of metastatic foci ($P = 0.0015$). MRSA = methicillin-resistant <i>Staphylococcus aureus</i> ; SSTI = skin and soft-tissue infection; UTI = urinary tract infection.			

Endocarditis

Patients underwent echocardiography, according to local guidelines, for the following indications: presence of prosthetic heart valves, clinical evidence of endocarditis, or community-acquired SAB. Of the 22 patients who underwent echocardiography, 7 (31.8%) had evidence of endocarditis; overall prevalence of echocardiograph-confirmed endocarditis was 7.1%. Of the three indications, clinical evidence for endocarditis was the only significant predictor of echocardiograph-confirmed endocarditis, with a sensitivity and specificity of 57.1% (95% confidence interval (CI), 18.4 to 90.1) and 93.3% (95% CI, 86.1 to 99.8) respectively, amongst the study sub-population who had indications for echocardiography (Table 2).

Table 2: Echocardiograph testing.

		Echocardiograph Result		Total	P-value
		Positive	Negative		
Clinical endocarditis	Yes	4	1	5	0.020
	No	3	14	17	
Prosthetic material	Yes	1	0	0	0.318
	No	6	15	21	
CA vs HCA	CA	4	4	8	0.342
	HCA	3	11	14	

Antibiotic management

An empiric antibiotic with adequate activity and dose for SAB was prescribed in 45 (47.9%) cases. Empiric antibiotic choices included carbapenems in 24%, third generation cephalosporins in 17%, beta-lactam/beta-lactamase inhibitors in 15%, vancomycin in 20%, cloxacillin in 14%, aminopenicillins in 2%, quinolones in 4%, and aminoglycosides in 5%. Median time to definitive therapy from the initial blood culture was 51.5 hours (IQR 41 to 67; range 4 to 156), with no significant difference between HCA and CA ($P = 0.47$) or between MSSA and MRSA infections ($P = 0.28$, Figure 2). Time to definitive therapy was not associated with complicated infection or mortality on multivariate analysis (Table 3). Empiric antibiotic therapy was non-optimal in 52.1% of all cases, and in 90.9% of those with MRSA bacteraemia. Definitive antibiotic therapy was non-optimal in 22.6% of all cases, and in 35.3% of those with MRSA bacteraemia. Median duration of therapy was 14 days for both MSSA and MRSA

bacteraemia (IQR 5 to 16). Of the MRSA-infected patients, 21 (64.7%, $n = 33$) received a vancomycin loading dose. Therapeutic drug monitoring of vancomycin was performed on at least one occasion in all but one case, at a median of 48 hours (IQR 24 to 72) after the initial dose. The vancomycin trough concentration ranged from below the lower limit of detection to 48.9 $\mu\text{g/mL}$, with 8 (47%) cases below the recommended target of 15 $\mu\text{g/mL}$. Source control

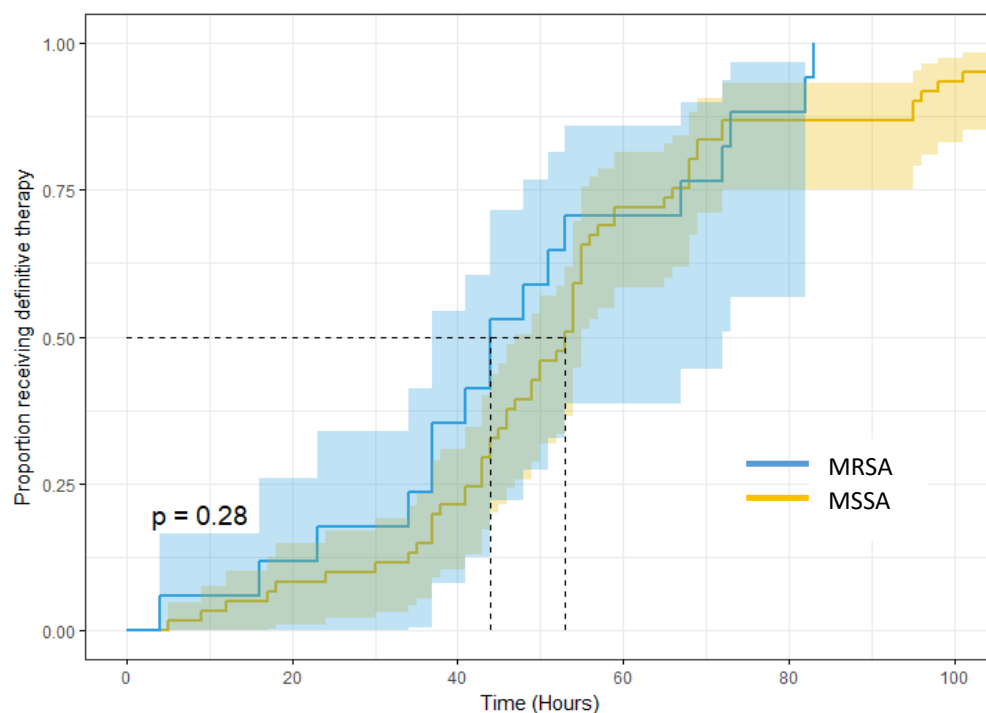


Figure 2 Kaplan Meyer (KM) plot for time to definitive antibiotic therapy, stratified by MRSA and MSSA. 95% CI indicated by shaded region.

was potentially indicated for 36 patients, and was performed in 21 (58.8%).

Outcomes

Inpatient and 90-day mortality was 41.8% (95% CI, 31.9 to 52.2) and 47.0% (95% CI, 36.9 to 57.2), respectively, with 30 (83.3%, $n = 36$) deaths attributable to SAB. The unadjusted survival estimates are shown in Figure 3; median time to death was 35 days (IQR 17 to 62).

There was a strong trend towards increased 90-day mortality with the presence of co-morbidities (OR 4.1; 95% CI 1.0 to 21.6; $P = 0.06$) and MRSA infection (OR 3.6; 95% confidence interval (CI) 1.0 to 15.1; $P = 0.06$) on multivariable regression analysis (Table 3).

SAB was complicated by persistent infection (blood culture positive ≥ 72 hours on therapy), deep abscess formation, or endocarditis in 30 (31.6%, $n = 95$) cases. The odds of

complicated infection were higher with non-optimal definitive antibiotic therapy (OR 8.5; 95% CI 1.8 to 52.4), female sex (OR 3.8; 95% CI 1.1 to 16.3) and community-acquired infection (OR 7.4; 95% CI 2.0 to 33.1) (Table 3).

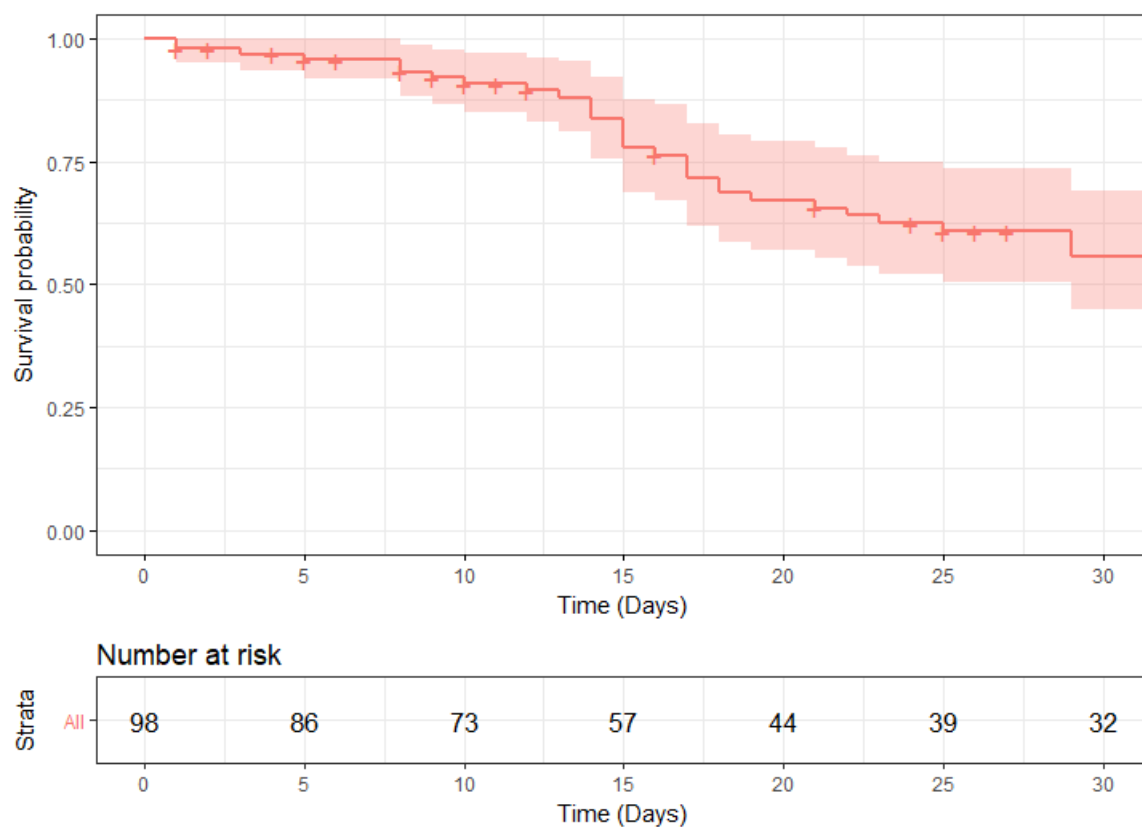


Figure 3 Kaplan Meier (KM) survival plot for inpatient mortality. 95% CI indicated by shaded region.

Table 3. Univariate and multivariate logistic regression analysis for a) 90-day mortality, and b) complicated infection.

a) Mortality						
	Univariate analysis			Multivariate analysis		
Covariate	OR	95% CI	<i>P</i> -value	OR	95% CI	<i>P</i> -value
Age > 60 years	3.3	1.3 – 8.7	0.01*	2.6	0.8 – 8.9	0.1
Female sex	0.6	0.3 – 1.6	0.3	0.5	0.2 – 1.7	0.28
MRSA	2.3	0.9 – 6.1	0.08	3.6	1.0 – 15.1	0.06
Community-acquired infection	1.6	0.7 – 4.0	0.3	0.9	0.3 – 2.9	0.89
Non-optimal definitive AB therapy	0.7	0.2 – 2.0	0.5	0.66	0.1 – 2.7	0.56
Co-morbidity present	3.9	1.3 – 14.6	0.03*	4.07	1.0 – 21.6	0.06
HIV	1.1	0.4 – 3.2	0.9			
Renal Failure	2.7	1.1 – 6.8	0.03*			
Cardiovascular disease	1.1	0.5 – 2.6	0.9			
Time to definitive therapy	1.0	0.9 – 1.1	0.5	1	0.9 – 1.1	0.81
Time to notification of results	1.0	0.9 – 1.1	0.2			
b) Complicated infection						
	Univariate analysis			Multivariate analysis		
Covariate	OR	95% CI	<i>P</i> -value	OR	95% CI	<i>P</i> -value
Age > 60 years	0.7	0.3 – 1.9	0.5	0.9	0.2 – 3.0	0.8
Female sex	1.8	0.2 – 1.9	0.2	3.8	1.1 – 16.3	0.05*
MRSA	1.3	0.5 – 3.6	0.5	0.9	0.2 – 3.5	0.9
Community-acquired infection	2.7	1.1 – 6.8	0.03*	7.4	2.0 – 33.1	0.01*
Non-optimal definitive AB therapy	1.5	0.5 – 4.3	0.4	8.5	1.8 – 52.4	0.01*
Co-morbidity present	0.8	0.3 – 1.9	0.7	2	0.5 – 9.9	0.36
HIV	0.6	0.2 – 1.9	0.4			
Renal Failure	0.9	0.3 – 2.3	0.8			
Cardiovascular disease	1.5	0.6 – 3.8	0.4			
Time to definitive therapy	0.97	0.95 – 1.0	0.03*	1	0.9 – 1.1	0.2
Time to notification of results	1.0	0.9 – 1.1	0.7			

* $p \leq 0.05$

DISCUSSION

Complicated infection and SAB-related mortality were high in this well-characterized clinical cohort from South Africa. Most infection episodes were health care-associated and related to intravenous peripheral catheter infection, suggesting that many were preventable. Of concern, definitive antibiotic therapy was non-optimal in almost a quarter of cases, and this was strongly associated with complicated infection.

At 47%, all-cause mortality was similar to that found in other studies from South Africa (Perovic et al., 2006; Smidt et al., 2015) and other LMICs (Nickerson et al., 2009), but was substantially worse than in high income countries, where mortality ranges between 20 and 30% (Braquet et al., 2017; Kaasch et al., 2014; Laupland et al., 2008). This may be related to the high prevalence of comorbidities and MRSA infection in our population, both of which have been associated with an increased risk of mortality with SAB (Allard et al., 2008; P Braquet et al., 2016; Cosgrove, 2006; Naidoo et al., 2013). Although the short-term outcomes of medical patients at Groote Schuur Hospital are generally poor, with only 65% surviving to 12 months post-discharge (Stuart-Clark et al., 2012), this does not fully explain the poor early outcomes observed in our study, where the majority of deaths were possibly SAB-related. Over a fifth of our patients had HIV-co-infection, but this was not associated with mortality or complicated infection, in contrast to other reports (Jaliff et al., 2014). This suggests that specific host- or pathogen-related factors may account for the worse outcomes observed compared to other settings.

Around a third of our patients were assessed as having complicated infection, which is lower than that described in a large cohort from the US (43%) using similar definitions (Fowler et al., 2003). There are limited data on rates of complicated SAB, likely due to inconsistent definitions and the difficulties in ascertaining this outcome, allowing limited conclusions from direct comparisons. Half of the community-acquired infections in our cohort presented with metastatic foci, supporting previous reports of community-acquired infection as a clinical predictor of complicated infection (Fowler et al., 2003), presumably due to later presentation and treatment. As observed in other settings (Smit et al., 2017), female patients were found to be at increased risk of complicated infection, suggesting that sex may need to be considered when risk-stratifying patients. This association is likely multifactorial, and subject to the confounders present in observational studies. However, it has been speculated

that distinct sex differences in immune responses to infection may play a role (Humphreys, Fitzpatrick, & Harvey, 2015). The only modifiable factor associated with complicated SAB in our cohort was the administration of non-optimal antibiotic therapy, which is of concern.

Administration of optimal empiric and directed antibiotic therapy has an important influence on the outcomes of both MSSA and MRSA (Van Hal et al., 2012); in one study, administration of adequate initial therapy for MRSA bacteraemia was shown to confer an almost 2-fold survival benefit (OR, 1.84; 95% CI 1.25 to 2.71) (Paul et al., 2010). Definitive antibiotic therapy was non-optimal in almost a quarter of our patients, and in a third of those with MRSA. The inadequacy of both empiric and definitive antibiotic therapy, especially for MRSA infections, possibly contributed to the trend of increased 90-day mortality associated with MRSA bacteraemia. An additional concern is that when indicated, early source control was performed in fewer than 60% of cases. These findings clearly identify a need for improved management of SAB in our setting. Surveys of South African medical students have found a low level of antibiotic knowledge, including for the treatment of SAB (Wasserman et al., 2017), and this should have a greater emphasis in both undergraduate and postgraduate medical training as a measure to improve SAB management. The involvement of Infectious Diseases (ID) specialists and use of bedside management protocols are an important aspect of SAB care: recommended management strategies are carried out significantly more frequently among patients assessed by an ID specialist, contributing to the survival benefit associated with this intervention (Liu, 2013; Paulsen et al., 2015; Vogel et al., 2016). Although all patients in our study were followed up by members of the ID Division, we did not evaluate adherence to management advice. Most South African hospitals do not have access to ID specialists, but should consider implementing evidence-based bundle interventions, including early source control, and early use of intravenous cloxacillin. These are simple and cheap to implement, and result in mortality reduction for SAB (López-Cortés et al., 2013).

In contrast to high-income countries, where the highest case burden of SAB is seen in the elderly (K. Laupland et al., 2013), only 28% of our cohort was over the age of 60 years. This may reflect the higher incidence of comorbidities, such as HIV, in younger members of our population. Similarly to other settings, (Allard et al., 2008; Asgeirsson, Gudlaugsson, Kristinsson, Heiddal, & Kristjansson, 2011; Huggan et al., 2010; Kleven et al., 2007) a high proportion of SAB cases were healthcare-associated. This is related to increased exposure to

intravascular access devices, including short-term peripheral venous catheters, which are an important cause of bloodstream infection (Mermel, 2017). Our finding that the majority of SAB episodes were related to peripheral venous catheter use emphasizes the need for improved infection prevention practices in local healthcare settings, such as the implementation of evidenced-based bundles of care to reduce intravascular line infection (Fitzgerald et al., 2017; Larsen et al., 2012; Wilson, Moore, Lucas, Francis, & Gebo, 2008).

The prevalence of endocarditis in our study was 7%, similar to the proportion of SAB with endocarditis in the United States (Klevens et al., 2007). While some form of echocardiography is generally recommended for all patients with SAB (Holland et al., 2014), this is not always feasible in low resource settings, particularly for transesophageal echocardiography which has a higher yield than transthoracic imaging. Clinical guidelines may be a useful strategy to identify low risk patients not requiring echocardiography. Although our study was not designed to evaluate this, and the denominator was small ($n = 22$), echocardiography testing according to local guidelines, namely those patients with implanted prosthetic heart valves, clinical evidence of endocarditis, or community-acquired infection, was able to identify endocarditis with an accuracy of 72.7%. Only one case was diagnosed on echocardiography in the absence of these indications, suggesting that these clinical indicators are useful in ruling out endocarditis. However echocardiography was not performed on the entire study population, and the results are therefore not necessarily generalisable to all patients with SAB. Future studies should be undertaken to define better the indications for echocardiography for SAB in LMICs.

The proportion of our patients with MRSA infection, at 24%, was lower than that reported from South African tertiary hospitals in Gauteng from a similar period (36%) (Smidt et al., 2015), but is on par with other results from local state sector hospitals at earlier periods (Naidoo et al., 2013; Perovic et al., 2006), suggesting that the incidence of MRSA bacteraemia is stable. However, local rates of HCA-MRSA are substantially higher than those reported in high-income countries, which are generally under 10% (Forsblom et al., 2011; Tom, Galbraith, Valiquette, & Jacobsson, 2014). This reflects challenges in infection prevention and control (IPC) services in South African public hospitals, many of which do not have antibiotic stewardship programs or dedicated IPC nurses. As expected, almost all MRSA cases were healthcare-associated, reflecting the absence of the ST8:USA300 strain of community-

associated MRSA in South Africa (Goering et al., 2008). However, there were a small number of cases of community-acquired MRSA bacteraemia in our cohort, emphasizing the need for clinician awareness and ongoing microbiological surveillance with accurate ascertainment of site of SAB acquisition (CA versus HCA).

Despite definitive treatment being delayed by 24 hours or more from initial blood culture in most patients, this was not associated with an increased risk of mortality, as has been observed in other studies (Lodise et al., 2003; Marchaim et al., 2010). It is possible that the negative impact of delayed therapy might have been more clearly seen if a higher proportion of cases had received optimal definitive treatment, or if the levels of antibiotic resistance were higher, with decreased adequacy of empiric antibiotic therapy. This delay in definitive treatment reflects a delay in the identification and susceptibility profiling of *S. aureus* from positive blood cultures. The use of novel tools to identify *S. aureus* directly from blood cultures, such as fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), immunochromatographic assays for PBP2a and other methods have been shown to quickly and reliably identify *S. aureus* (Buchan et al., 2015; Delport et al., 2016; Felsenstein et al., 2016; Oliveira, Procop, Wilson, Coull, & Stender, 2002; Thomas, Gidding, Ginn, Olma, & Iredell, 2007). The use of such tools in our setting could be valuable in encouraging prompt antimicrobial treatment of SAB and an improvement in patient outcomes, although cost may be an important limiting factor.

While the management of SAB in our setting is inevitably affected by organizational level factors, resulting in delays of organism identification and reduced rates of echocardiography, the results of this study can be used to inform management strategies in various ways. On a clinician level, improved knowledge regarding recognition and treatment of SAB, especially infections with MRSA, is key. While infectious disease consultation and guidance is important, so too is ensuring that the advice is followed, and that the patient receives the medication. More regular input is required with drugs such as vancomycin, as it requires a loading dose and additional monitoring. Clinicians should be actively encouraged to seek guidance when prescribing antibiotics. The high proportion of infections related to intravenous cannulas highlights the importance of intravenous cannula care and monitoring, both as a prevention strategy and as a part of source control.

The major strength of this study was our ability to accurately evaluate the setting of infection acquisition, and prospectively capture well-defined clinical outcomes and management practices. There were, however, a number of important limitations. The relatively small sample size resulted in reduced statistical power and generalizability. Because of this, important risk factors in the greater South African population may not have been detected in this cohort. For example, because source control was only indicated in 36 patients, this variable was not included in our prediction models. It is possible that the use of the electronic notification system may have resulted in cases of SAB during the study period being missed, which could have biased our findings if the loss was non-random. SAB incidence has been shown to vary between hospitals within South Africa (Smidt et al., 2015), which may further reduce the external validity of the results of this single-site study. Future studies should attempt standardized collection and analysis of pooled data from various hospitals across South Africa, with a particular focus on SAB management

CONCLUSIONS

SAB is strongly related to intravenous peripheral catheter infection in our setting, and mortality is notably higher relative to higher-income countries. Non-optimal antibiotic management, especially for MRSA, is a significant problem and may contribute to these poor outcomes. Cost-effective prevention and treatment strategies should be implemented as a priority to reduce the burden of SAB in South African public hospitals.

Acknowledgements

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Conflicts of interest

All authors report that they do not have a commercial or other association that might pose a conflict of interest.

Sources of funding

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Part D. Appendix

A. SAB Database Clinical Capture Form V7

PATIENT LABEL		Tel:
Date of admission		
Admitting team & ward		
HIV status & CD4		
Co-morbidities		
Active drip site sepsis		
Presenting problem		

MICROBIOLOGY

Initial blood culture date/time			Incubation time
MRSA vs MSSA			
Vancomycin MIC			
Antibiogram (circle if resistant)	Penicillin Clindamycin	Moxifloxacin Fusidic acid	Cotrimoxazole Rifampicin
Date and time of result notification		Timing after initial BC (hrs):	

REPEAT CULTURES AFTER INITIAL CULTURE

	1	2	3	4	5
Date					

Time					
Result					
Calculated time in hours					

CULTURES AFTER START OF DEFINITIVE TREATMENT

	1	2	3	4	5
Date					
Time					
Result					
Calculated time in hours					

TIME TO NEGATIVE CULTURE

From initial BC	
From definitive treatment	

RISK FACTORS FOR COMPLICATIONS

Source of infection	
CA vs HCA	
Clinical endocarditis	
Metastatic foci <ul style="list-style-type: none"> – Endocarditis – Pulmonary – Bone – Deep abscess – Meningitis 	
Prosthetic material <ul style="list-style-type: none"> – Joint – Endovascular 	
Other complications <ul style="list-style-type: none"> – Other HCAI – CDI 	

– DVT	
-------	--

ECHO AND OTHER TESTS

TTE vs TOE		
Date performed		Time after initial BC (hrs):
Findings		
Other tests and findings		

THERAPY

Empiric		
Definitive/appropriate <ul style="list-style-type: none"> – Cloxacillin 2/3g – Vancomycin – Other 		Date and time started:
Vancomycin LD (yes/no)		
Time to definitive (after initial BC)		
Total duration		
Source control		
Initial vanco trough level	Timing:	Value:
Complications of therapy		

OUTCOMES

Alive at discharge	
Date of death/discharge	
Alive at 90 days	
Primary cause of death	

B. Letter of Approval from Human Research Ethics Committee



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



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 Groote Schuur Hospital
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 Website: www.health.uct.ac.za/fhs/research/humanethics/forms

20 July 2017

HREC REF: 517/2017

A/Prof Mary-Ann Davies
 Public Health & Family Medicine
 CIDER
 Falmouth Building
 Level 5, Entrance 5, Room5.39

Dear A/Prof Davies

PROJECT TITLE: THE MANAGEMENT AND OUTCOMES OF STAPHYLOCOCCUS AUREUS BACTERAEMIA AT A SOUTH AFRICAN REFERRAL HOSPITAL: A PROSPECTIVE OBSERVATIONAL STUDY. (Masters candidate- Ms N Steinhaus) SUB-STUDY LINKED TO 643/2015

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study subject to the annual approval of study 643/2015.

Approval is granted for one year until the 30 July 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Nicola Steinhaus will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
 Federal Wide Assurance Number: FWA00001637.

HREC 517/2017

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 517/2017

C. Instructions for Authors from International Journal of Infectious Disease

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Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double-blind) or the manuscript file (if single-blind). If there are no interests to declare then please state this: 'Declarations of interest: none'. This summary statement will be ultimately published if the article is accepted. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches. [More information](#).

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Authorship

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